Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2003-06

Pyraclostrobin
Headline EC
Cabrio EG

The active ingredient pyraclostrobin and associated end-use products, Headline EC, for the control of tan spot, septoria leaf spot, leaf rust, powdery mildew, spot blotch, and stripe rust in wheat; net blotch, scald, spot blotch and stripe rust in barley; leaf rust and powdery mildew in rye; ascochyta blight in chick peas; anthracnose and aschochyta blight in lentils; mycosphaerella blight and powdery mildew in dry field peas; anthracnose, powdery mildew and rust in dry beans *Phaseolus* spp.; anthracnose, mycosphaerella blight, powdery mildew and rust in dry beans *Vigna* spp.; mycoshaerella blight and powdery mildew in dry beans *Lupinus spp*.; and mycosphaerella blight and powdery mildew in faba beans; early blight and late blight in potatoes; Cercospora leaf spot and powdery mildew in sugar beets; stem and leaf rust and suppression of powdery mildew in bluegrasses, fescues and ryegrasses grown for seed; and, Cabrio EG, for the control of anthracnose and Phomopsis in highbush and lowbush blueberries; Alternaria purple blotch and downy mildew in Crop Group 3 bulb vegetables (onions (dry and green), garlic, leek and shallot); alternaria blight, anthracnose, downy mildew, powdery mildew and gummy stem blight in field cucumber, gherkin, muskmelon, pumpkin, citron melon, watermelon, winter squash, and summer squash; early blight and anthracnose in field peppers (bell, chili, cooking, sweet, pimento), eggplant, and field tomato; late blight in eggplant and field tomato; Alternaria, powdery mildew and Cercospora leaf spot in carrot, garden beet, turnip, rutabaga, oriental radish, radish and horseradish; suppression of Monilinia blossom and twig blight and control of anthracnose in stone fruits Crop Group 12 (apricot, cherry (sweet and tart), nectarine, peach, plums, and prune); control of powdery mildew in cherries (sweet and tart), and anthracnose in strawberries have been granted temporary registration under Section 17 of the Pest Control Products Regulations

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued temporary registrations for the fungicide pyraclostrobin, manufactured by BASF, and the associated end-use products, Headline EC, for the control of tan spot, septoria leaf spot, leaf rust, powdery mildew, spot blotch, and stripe rust in wheat; net blotch, scald, spot blotch and stripe rust in barley; leaf rust and powdery mildew in rye; ascochyta blight in chick peas; anthracnose and aschochyta blight in lentils; mycosphaerella blight and powdery mildew in dry field peas; anthracnose, powdery mildew and rust in dry beans Phaseolus spp.; anthracnose, mycosphaerella blight, powdery mildew and rust in dry beans Vigna spp.; mycoshaerella blight and powdery mildew in dry beans Lupinus spp.; and mycosphaerella blight and powdery mildew in faba beans; early blight and late blight in potatoes; Cercospora leaf spot and powdery mildew in sugar beets; stem and leaf rust and suppression of powdery mildew in bluegrasses, fescues and ryegrasses grown for seed; and, Cabrio EG, for the control of anthracnose and Phomopsis in highbush and lowbush blueberries; Alternaria purple blotch and downy mildew in Crop Group 3 bulb vegetables (onions (dry and green), garlic, leek and shallot); alternaria blight, anthracnose, downy mildew, powdery mildew and gummy stem blight in field cucumber, gherkin, muskmelon, pumpkin, citron melon, watermelon, winter squash, and summer squash; early blight and anthracnose in field peppers (bell, chili, cooking, sweet, pimento), eggplant, and field tomato; late blight in eggplant and field tomato; Alternaria, powdery mildew and Cercospora leaf spot in carrot, garden beet, turnip, rutabaga, oriental radish, radish and horseradish; suppression of Monilinia blossom and twig blight and control of anthracnose in stone fruits Crop Group 12 (apricot, cherry (sweet and tart), nectarine, peach, plums, and prune); control of powdery mildew in cherries (sweet and tart), and anthracnose in strawberries.

These products were reviewed jointly by Health Canada's Pest Management Regulatory Agency and the U.S. Environmental Protection Agency (U.S. EPA) within the North American Free Trade Agreement's Technical Working Group on Pesticides (NAFTA TWG) Joint Review Program.

Methods for analysing pyraclostrobin in environmental media are available to research and monitoring agencies upon request to the PMRA.

BASF will be carrying out additional studies as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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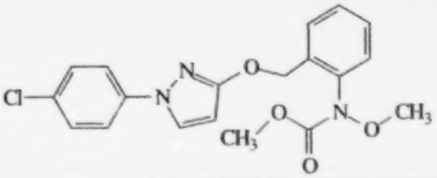
1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

Table 1 TGAI Identitification

Active substance	Pyraclostrobin
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	methyl N-{2-[1-(4-chlorophenyl)-1H-pyrazol-3-yloxymethyl]phenyl}(N-methoxy)carbamate
2. Chemical Abstracts Service (CAS)	methyl [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl]methoxycarbamate
CAS number	175013-18-0
Molecular formula	$C_{19}H_{18}ClN_3O_4$
Molecular weight	387.82
Structural formula	
Nominal purity of active	98.0% (limits 95.0–100%)

Identity of relevant impurities of toxicological, environmental or other significance	The technical grade pyraclostrobin does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track-1 substances as listed in App II of DIR99-03. It contains dimethyl sulfate (DMS) at a maximum level of 3 ppm which is listed by the International Agency for Research on Cancer (IARC) in Group 2A ("probable human carcinogen") and is classified as a "select carcinogen" under the criteria of Occupational Safety and Health Administration (OSHA) Laboratory Standard. The presence of DMS even in trace amounts in Headline EC and Cabrio EG is not possible due to the use of formulants which will hydrolyze this contaminant.

1.2 Physical and chemical properties of active substances and end-use product(s)

Table 2 Technical product: Pyraclostrobin

Property		Result	Comment
Colour and physical state		White to light beige	
Odour		Odourless	
Melting point/range		63.7–65.2	
Boiling point/range		N/A	
Density		1.285 g/cm^3 at 20°C	
Vapour pressure		Vapour pressure Temp. 2.6×10^{-10} hPa 20°C 6.4×10^{-10} hPa 25°C	Non-volatile from water and moist soil surface
Henry's Law constant at 20°C	1/H	5.821×10^{8}	
	K	4.3×10^{-11} atm. M^3/mole	
Ultraviolet (UV)/visible spectrum		$\lambda_{max} = 275$ nm	Minimal direct phototransformation is expected under natural environment

Property	**Result**	**Comment**
Solubility in water at 20°C	Solvent — mg/L Deionized water 2.41 Buffer system pH 7 1.9 Buffer system pH 4 2.3 Buffer system pH 9 1.9	Low solubility. One of the indicators of low potential to leach.
Solubility in organic solvents at 20°C	Solvent — mg/L acetone ≥160 methanol 11 2-propanol 3.1 ethyl acetate ≥160 acetonitrile ≥76 dichloromethane ≥110 toluene ≥100 n-heptane 0.36 1-octanol 2.4 olive oil 2.9 DMF ≥62	
n-Octanol/water partition coefficient K_{ow} at room temperature	pH — log K_{ow} — K_{ow} 6.5 4.18 15 136 6.2 3.80 6310	Potential for bioaccumulation
Dissociation constant	There are no dissociable moieties.	Does not dissociate in water.
Stability (temperature, metal)	Stable to normal and elevated temperature (54°C), aluminum, aluminum acetate and iron filings.	

Table 3 **End-use product:**
- **Headline EC**
- **Cabrio EG**

Property	**Headline EC**	**Cabrio EG**
Colour	Dark yellow	Light brown
Odour	Naphthalene	Not provided
Physical state	Liquid	Extruded granules
Formulation type	Emulsifiable concentrate	Wettable granules

Property	Headline EC	Cabrio EG
Guarantee	250 g/L nominal (limits 243–258 g/L)	20.0% nominal (limits 19.7–20.6%)
Formulants	These products does not contain any EPA List 1 formulants or formulants known to be TSMP Track-1 substances.	
Container material and description	Plastic	HDPE and nylon bags
Bulk density	1.055 g/cm^3	0.574 kg/L
pH of 1% dispersion in water	6.2–6.4	6.98
Oxidizing or reducing action	The product reacts mildly with potassium permanganate, does not react with iron or water and is non-hazardous when in contact with monoammonium phosphate.	The product is considered to be mild reducing agent and should not be mixed with or stored in close proximity to strong oxidizing agents. It does not react with water or iron.
Storage stability	The product is stable for 24 months at 20°C in commercial packaging.	The product is stable when stored for twelve months at warehouse temperature in commercial packaging.
Explodability	Not explosive	Not explosive
Identity of relevant impurities of toxicological, environmental or other significance	Contains a formulant which is on the EPA List 2 Potentially Toxic Inerts.	No known EPA list 1 or 2 formulants are contained in this formulation.

1.3 Details of uses

Headline EC (250 g a.i./L) is a fungicide exhibiting translaminar movement for use in pulses, wheat, barley, rye, potato, sugar beets and grasses grown for seed. It is proposed as preventative treatment to control a number of diseases including *Ascochyta* spp, *Colletotrichum* spp, *Phytophthora infestans*, *Erysiphe* spp and various other diseases using ground application on all approved crops and aerial application on chick pea, dry field peas, dry beans, faba beans, lentil, barley, rye and wheat. The maximum application rate is 900 g of product per hectare equivalent to 225 g a.i./ha. It will be marketed in 10 L containers.

Cabrio EG (20% a.i./kg) is a fungicide exhibiting translaminar movement for use in blueberry, onion, garlic, leek, shallot, field cucumber, gherkin, muskmelon, winter squash, pumpkin, watermelon, field tomato, field pepper, eggplant, carrot, garden beet, stone fruits and strawberry. It is proposed as a preventative treatment to control a number of diseases including Cercospora spp, Colletotrichum spp, Phytophthora infestans, Erysiphe spp and various other diseases using ground application only. The maximum application rate is 1000 g of product per hectare equivalent to 224g a.i./ha. It will be marketed in 5 kg bags.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Product	Analyte	Method ID	Method type	Linearity range µg/mL	Mean recovery	RSD (%)	Method
Technical	Active	CP 266	HPLC/UV at 275 nm	50.0–200.0	98.8	2	Acceptable
Technical	Major impurities	CP 337	HPLC/UV at 337 nm	0.85–42.48	91.1–106.7	3.8–6.3	Acceptable

2.2 Method for formulation analysis

Product	Method ID	Method	Linearity range (mg)	Recovery range (%) (n)	Standard deviation (n)	Method
Headline EC	CF-A 535	HPLC/ UV at 278 nm	39.3–127.9	99.9–100.3 (6)	0.085% (6)	Acceptable
Cabrio EG	CF-A 587	HPLC/ UV at 275 nm	0.0–50.0	100.4–101.7 (6)	0.40% (6)	Acceptable

2.3 Methods for residue analysis

2.3.1 Residue analysis of plants, plant products and animal matrices

see Appendix I for tables

2.3.2 Methods for environmental residue analysis

see Appendix I, Table 3

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

A detailed review of the toxicology database available for the new fungicide, pyraclostrobin, has been completed. The submitted studies were conducted in conformance with currently acceptable international testing protocols. However, the maximum tolerated dose (MTD) was not reached nor was the limit dose tested for the mouse and rat oncogenicity studies, the rat chronic study, the rat reproduction study and the 28-day rat dermal toxicity study.

Pyraclostrobin was rapidly, but incompletely, absorbed and rapidly excreted by the rat following oral administration. Pyraclostrobin was distributed to most tissues, but the radioactivity was < 1 ppm in each tissue after 120 hours. The primary route of excretion was via the feces accounting for 79% to 92% of the administered dose (AD). Urine and biliary excretion accounted for 11% to 16% and 45% to 50% of the AD, respectively. Pyraclostrobin was extensively metabolized resulting in the isolation of a number of metabolites from the urine and feces. The major metabolic pathways were N-demethylation and hydroxylation of the parent or glucuronide conjugates of a variety of phase I-type metabolites.

Acute dosing revealed that technical pyraclostrobin was of low toxicity by the oral and dermal routes, and was moderately toxic via the inhalation route. It was moderately irritating to the skin, minimally irritating when instilled into the eyes and was not a skin sensitizer (Maximization test). The Headline EC formulation was of high toxicity by the oral route, and of low toxicity by the dermal and inhalation routes. It was severely irritating to the skin and moderately irritating to the eyes but was not a dermal sensitizer (Buehler method). The Cabrio EG formulation, was of low toxicity by the oral, dermal and inhalation routes. It was slightly irritating to the skin, minimally irritating when instilled into the eyes and was not a skin sensitizer (Buehler method).

Short-term repeated dermal (28 days) dosing in rats with technical pyraclostrobin did not result in any treatment-related systemic effects up to and including the highest dose level tested of 250 mg/kg body weight/day (bw/d). However, local dermal irritation was observed at dose levels of 100 mg/kg bw/d and higher.

The target organ for all species tested, after short-term exposure to technical pyraclostrobin, was the duodenum. In mice, thickening of the mucosa of the duodenum was observed at 30.4/40.4 mg/kg bw/d and higher, duodenal hyperplasia was seen in the rat at doses of 9.0/9.6 mg/kg bw/d and higher and mucosal hypertrophy of the duodenum was seen in dogs at the high dose of 12.9/13.6 mg/kg bw/d. In mice, ulcers/erosions of the glandular stomach were observed at doses of 30.4/12.9 mg/kg bw/d and higher after short-term exposure, but were not seen after long-term exposure at doses up to and including the high dose of 17.2/32.8 mg/kg bw/d. In rats, acanthosis and ulceration of the forestomach and erosions/ulcers of the glandular stomach were observed in males after long-term exposure only, at the high dose of 9.2 mg/kg bw/d. However, all but the incidence of ulceration of the glandular stomach fell within the historical control range of values and so the toxicological significance of these findings is uncertain. Other findings after short-term exposure for mice were thymus atrophy and apoptosis of the lymph nodes at doses of 30.4/40.4 mg/kg bw/d and higher; decreased WBC count at 274.4/162.9 mg/kg bw/d and higher; clinical chemistry findings at 30.4/40.4 mg/kg bw/d and higher; and decreased body weight and food intake at 119.4/162.0 mg/kg bw/d and higher. For rats, additional findings included increased spleen weight and splenic extramedullary hematopoiesis at 68.8/79.7 mg/kg bw/d and higher; sinus distension and histiocytosis of the spleen at 10.7/12.6 mg/kg bw/d and higher; increased liver weight and hepatocyte hyperplasia for females at the high dose of 118.9 mg/kg bw/d; increased bilirubin at doses of 68.8/79.7 mg/kg bw/d and higher; and lower body weight gain at the high dose of 105.8/118.9 mg/kg bw/d. For dogs, lower body weight gain (females only) and clinical chemistry findings were seen at 10.8/11.2 mg/kg bw/d and higher.

Adverse treatment-related effects after chronic exposure to pyraclostrobin were not observed in mice or rats up to and including the highest dose levels tested of 17.2/32.9 mg/kg bw/d, and 9.0/12.3 mg/kg bw/d, respectively.

Since MTDs were not attained in the life-time studies, it is unknown if and when the duodenal hyperplasia observed after short-term exposure in the rat would progress to duodenal neoplasia. However, it can be concluded that there is no evidence of oncogenic potential of pyraclostrobin in mice and rats at dose levels up to 17.2/32.8 mg/kg bw/d and 9.2/12.6 mg/kg bw/d, respectively. The in vitro and in vivo mutagenicity assays conducted yielded negative results for genotoxic potential.

Pyraclostrobin did not affect reproductive performance or reproductive parameters at any dose level tested. There were no toxicologically significant effects noted for parental animals. For offspring, the only treatment-related finding was slightly lower pup body weight for F1 and F2 pups on days 7, 14 and(or) 21 post partum, which was not considered adverse. Increased susceptibility of pups was not demonstrated in this study. However, dose levels chosen were not high enough to adequately assess potential reproductive effects or susceptibility of pups.

Pyraclostrobin was not fetotoxic/teratogenic to rat fetuses at dose levels up to and including 50 mg/kg bw/d. Maternal findings were noted at 25 mg/kg bw/d and higher, manifest as decreased body weight gain and food intake. There was no evidence for increased susceptibility of rat fetuses following in utero exposure to pyraclostrobin. Pyraclostrobin was teratogenic to rabbit fetuses at the high dose of 20 mg/kg bw/d manifest as an increased incidence of fetal/litter skeletal malformations, specifically absent/misshapen lumbar vertebrae. Additional developmental findings were an increased incidence of resorptions and total litter loss at 10 mg/kg bw/d and higher, and increased post-implantation loss and decreased litter size at 20 mg/kg bw/d. Maternal findings were noted at 10 mg/kg bw/d and higher (decreased body weight gain and decreased gravid uterus weight). These findings indicate an increase in the qualitative susceptibility of the prenatal development of rabbit fetuses following in utero exposure to pyraclostrobin.

Pyraclostrobin showed no evidence of neurotoxicity in rats by either acute or subchronic exposure up to and including the highest dose levels tested of 1000 mg/kg bw/d in the acute study and 49.9/111.9 mg/kg bw/d in the subchronic study.

Additional studies will be requested in order to fully assess the toxicological profile, oncogenic potential and potential reproductive effects of pyraclostrobin (see Section 9.0).

3.2 Determination of acceptable daily intake (ADI)

An MTD was not attained in the mouse oncogenicity study, rat oncogenicity study, rat chronic study, rat reproduction study and 28-day dermal toxicity study. In the absence of these data at appropriate doses, a definitive ADI could not be determined. However, based on the absence of adverse effects in these studies at the doses tested, it is considered appropriate to conduct an interim risk assessment based on a margin of exposure (MOE) approach. The toxicological endpoint considered most appropriate for chronic/oncogenic risk assessment is duodenal hyperplasia, which was consistently seen in rats following short-term exposure. Hyperplasia is known to be a precursor event which may progress to neoplasia following long-term exposure. The lowest NOAEL for duodenal hyperplasia was 9.0/9.6 mg/kg bw/d, which was seen in the 28-day rat dietary study. However, all genotoxicity studies yielded negative results, indicating that pyraclostrobin is non mutagenic. The PMRA therefore considered that for an interim period of 5 years (i.e., until repeated cancer data is generated), an MOE of 3000× (i.e., 10× for interspecies differences, 10× for intraspecies differences, 10× for data deficiencies and 3× for the increase in the qualitative susceptibility of the rabbit fetuses) would provide an adequate margin of safety for this endpoint.

3.3 Acute reference dose (ARfD)

For an acute reference dose for females 13+ years, the study considered most appropriate in the submitted toxicological data base is the rabbit teratology study. The dose and endpoint selected for risk assessment is 5 mg/kg bw/d (increased resorptions/litter and increased total resorptions, i.e., dams with complete litter loss, at 10 mg/kg bw/d). For the calculation of the ARfD, an uncertainty factor (UF) of 300 is proposed. This is based on the standard uncertainty factor of 100 with an additional 3-fold uncertainty factor due to the severity of the toxicological endpoint.

The ARfD proposed is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{SF}} = \frac{5\ \text{mg/kg bw/d}}{300}$$

$$= 0.017\ \text{mg/kg bw/d mg/kg bw/d of pyraclostrobin.}$$

3.4 Toxicological endpoint selection—occupational and bystander risk assessment

The target organ of technical pyraclostrobin after subchronic oral exposure in mice, rats and dogs was the duodenum. Thickening and hypertrophy of the mucosa were seen in mice (30.4/40.4 mg/kg bw/d) and dogs (12.9/13.6 mg/kg bw/d), respectively. In rats, the more severe lesion of mucosal hyperplasia (9.0/9.6 mg/kg bw/d) was observed, which can potentially progress to neoplasia after continuous exposure. Duodenal hyperplasia is not expected to be observed after dermal or inhalation exposure since this finding was seen in the mucosal layer of the duodenum only, indicating that this lesion is the result of direct exposure of the duodenum to pyraclostrobin after oral administration. This is supported in part by the results of the 28-day oral and dermal rat studies, where hyperplasia of the mucosa of the duodenum was observed at 9.0 mg/kg bw/d and higher in the oral study, but was not observed in the dermal study at doses up to and including 250 mg/kg bw/d. Although MTDs were not attained in the mouse and rat long-term studies, there was no evidence of oncogenic potential of pyraclostrobin up to the highest dose levels tested of 17.2/32.8 mg/kg bw/d (mice) and 9.2/12.6 mg/kg bw/d (rats). Therefore, in the absence of actual data at higher doses, the NOAEL for possible tumour induction is ≥ 9.2 mg/kg bw/d. In addition, all of the in vitro and in vivo genotoxicity assays yielded negative results, indicating that pyraclostrobin is not mutagenic. Since the proposed exposure scenario is intermittent short-term/intermediate term, and includes only the dermal and inhalation routes of exposure, the mucosal hyperplasia of the duodenum is not considered to be an endpoint of concern.

Pyraclostrobin resulted in an increase in the qualitative susceptibility of the pre-natal development of rabbit fetuses, based on an increased incidence of resorptions, post-implantation loss and decreased litter size. Pyraclostrobin was also teratogenic to rabbit fetuses (absent/misshapen lumbar vertebrae) at maternally toxic doses. Pyraclostrobin was not fetotoxic/teratogenic to rat fetuses. The MTD was not attained in the reproductive study and so it was not possible to adequately assess potential reproductive effects or susceptibility of pups.

The exposure scenario for mixers, loaders and applicators and re-entry workers is intermittent and short-term to intermediate-term in duration, via the dermal and inhalation routes. Although a 28-day repeat dose dermal study is available, it is not considered adequate for occupational and bystander risk assessment. No effects were observed up to the highest dose tested of 250 mg/kg bw/d, which is well below the limit dose of 1000 mg/kg bw/d. It is therefore unknown whether there are systemic effects at higher doses. An appropriate inhalation study was not available for risk assessment. Because of the developmental toxicity seen in rabbits (which is not assessed in the 28-day dermal toxicity study), it is recommended that the rabbit developmental study be used for the occupational risk assessment. The recommended NOAEL is 5.0 mg/kg bw/d. An additional uncertainty factor (3×) in addition to the standard uncertainty factor of 100× is warranted based on the evidence of increased susceptibility of fetuses exposed in utero to pyraclostrobin.

3.5 Impact on human and animal health arising from exposure to the active substance or to its impurities

3.5.1 Operator exposure assessment

Cabrio EG Fungicide is formulated as a wettable granule (20% active guarantee) and is proposed for use as a fungicide for application to a variety of bulb vegetables, cucurbit vegetables, fruiting vegetables, root vegetables, berries, stone fruits and strawberries. Cabrio EG Fungicide may be applied by ground equipment. Farmers may mix, load and apply to all crops. Typical areas treated per day range from 4 to 40 ha for farmers. The proposed label specifies that mixer/loaders and applicators wear gloves (rubber, PVC, neoprene or nitrile), long sleeved shirt, trousers, shoes plus socks. Maximum rates of application range from 134 to 224 g a.i./ha. Farmers, mixing/loading and applying Cabrio EG Fungicide would typically be exposed once every 7–21 days, up to six times during the growing season (ie. 1–6 days per season, intermittent, short-term exposure).

Headline EC Fungicide is formulated as an emulsifiable concentrate (250 g a.i. per litre) and is proposed as a fungicide for application to wheat, barley, rye, chick peas, lentils, field peas (dry), beans (dry), potatoes, sugar beets and grass grown for seed. The label for Headline EC Fungicide also allows for application by ground or by air. Farmers may mix, load and apply to all accepted crops. Fungicides are also applied by custom applicators to wheat, barley, rye, chick peas, lentils, field peas (dry), field beans (dry), grass grown for seed and potatoes. Headline EC Fungicide is packaged in 104 L totes and 6.5 L jugs. The label for Headline EC Fungicide specifically states that the 6.5 L jug is intended for applicators treating less than 130 ha/d and if applicators are treating more than 130 ha/d, they must use the 104 L totes. The 104 L totes support a closed mixing and loading system. Typical hectarages treated per day range from 45 to 142 ha for farmers and up to 400 ha for custom applicators. It is specified on the label that goggles or face shield, gloves (rubber, PVC, neoprene or nitrile), hat, long-sleeved shirt, trousers and rubber boots are worn during clean-up, repairs, mixing and loading. Maximum rates of application range from 100 to 225 g a.i./ha. Farmers would typically be exposed one to six days during the growing season (i.e., short term exposure). Custom applicators could be exposed intermittently throughout the growing season (ie. intermediate exposure).

There is a potential for post-application exposure to workers irrigating, thinning, tying, staking, training, scouting, hand pruning, hand weeding and hand harvesting treated crops. Re-entry workers could be exposed intermittently throughout the growing season (i.e., intermediate exposure).

Dermal absorption
A chemical-specific in vivo dermal absorption study entitled *Study of Dermal Absorption in Rats*, was submitted. A significant limitation noted in the review of this study was that a large proportion of the dose was retained on the dressings. Therefore, the percentage absorbed was calculated as a percentage of the available dose (ie. applied dose minus dose remaining on dressings), as opposed to the percentage of the administered dose. This

would more accurately reflect the degree of absorption. The percentage absorbed is defined as the sum of blood, carcass, cage wash, cage wipe, urine, faeces and residues retained at the skin site (application site and surrounding skin).

A dermal absorption value of 50% was established from the chemical specific study based on the percentage of available dose absorbed following 24 hours of exposure to a nominal dose of 0.375 mg/cm^2. This value is considered conservative since the exposure period (24 hours) is greater than anticipated in the field and a significant proportion of the percentage of available dose absorbed (46.75%) is retained in the skin-bound residues which is not expected to become systemically available in total.

Due to the limitations in the dermal absorption study, it was considered appropriate to establish a dermal absorption value based on a weight-of-evidence approach. Taking into consideration the submitted dermal absorption study, the physical–chemical properties of pyraclostrobin and the toxicity studies for Headline EC and Cabrio EG, the dermal absorption value of 50% was retained for Headline EC and the dermal absorption value for Cabrio EG was lowered to 25%.

Exposure assessment

Pesticide Handlers' Exposure Database (PHED Version 1.1) assessments were conducted to derive estimates of occupational exposure for mixer/loaders and applicators. The data were based on high confidence PHED runs, adequate numbers of replicates and A+B grade data except for the groundboom applicator, closed cab scenario where A+B+C grade data were used. The PHED estimates generated generally conform with NAFTA Guidelines for using and reporting PHED data. PHED data does not provide exposure estimates for clean-up/repair activities nor quantify the variability of exposure estimates. Exposure via the inhalation route was a minor component of overall exposure. Total systemic exposure was determined by summing dermal deposition estimates (adjusted for dermal absorption) and inhalation estimates.

Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part which is most appropriate to the distribution of data for that body part. Exposure estimates for closed and open mixing and loading of Headline EC were derived for individuals wearing a single layer of clothing (long-sleeved shirt and long pants) and gloves. For groundboom and aerial applicators, estimates were derived for individuals wearing a single layer of clothing and no gloves. For custom groundboom application, exposure estimates were derived for closed mixing and loading and a closed cab scenario. Since the label specifically states that applicators treating more than 130 ha/d must use the 104 L totes (closed mix/load system), the closed mixing and loading scenario was used for custom applicators. For applications performed by the farmer, exposure estimates were derived for open mixing and loading and an open cab scenario. For Cabrio EG, exposure estimates were derived for individuals wearing a single layer of clothing and gloves, with the exception of the groundboom applicator in which exposure was estimated for applicators not wearing gloves. Exposure estimates and margins of exposure derived for mixer/loader/applicators of Headline EC and Cabrio EG are presented in Appendix II, Tables 2 and 3, respectively.

These margins of exposure are acceptable.

3.5.2 Bystanders

For the proposed agricultural use scenario, bystander exposure during and after application was considered minimal compared to mixer/loader/applicator and re-entry worker scenarios and, therefore, not quantified.

3.5.3 Workers

There is potential for intermittent intermediate-term exposure to workers handling Cabrio EG Fungicide and Headline EC fungicide-treated crops throughout the season.

The applicant submitted four dislodgeable foliar residue (DFR) studies (strawberries, peaches, grapes and peanuts) and one study comparing the effects of two different formulations of pyraclostrobin on dislodgeable foliar residues (grapes). All studies were reviewed and determined to be acceptable for risk assessment purposes.

Crop-specific studies were used for the post-application assessment of peaches, strawberries and grapes. The strawberry DFR study was used as a surrogate study for the post-application assessment of field tomatoes, green onions, carrots, field cucumbers and lowbush blueberries, the grape DFR study was used was used as a surrogate study for the post-application assessment of highbush blueberries and the peanut DFR study was used as a surrogate study for the post-application assessment of potatoes, wheat, barley, rye, chick peas, lentils, field peas and beans (dry) and sugar beets. Based on the dissipation of residues observed in these studies, appropriate transfer coefficients, an 8-hour workday, a 50% dermal absorption value for Headline EC, a 25% dermal absorption value for Cabrio EG and a NOAEL of 5 mg/kg bw/d, crop-specific re-entry intervals were established. Margins of exposure are acceptable for workers re-entering treated areas after the re-entry interval has elapsed. These re-entry intervals are presented in Appendix II, Tables 4 and 5.

Since the re-entry interval for hand harvesting of field beans and peas (dry) is shorter than the proposed pre-harvest interval of 30 days, a re-entry interval for hand harvesting of field beans and peas (dry) is not required.

These re-entry intervals are considered feasible from an agronomic perspective.

Since the re-entry interval for hand harvesting of bulb vegetables is shorter than the proposed pre-harvest interval of 7 days, a re-entry interval for hand harvesting of bulb vegetables is not required.

The 1–3 day re-entry intervals are considered feasible from an agronomic perspective. The 29-day re-entry interval for highbush blueberries is considered feasible as activities other than harvesting which require intensive foliar contact (pruning, thinning) do not typically occur during the application window and early season applications are recommended. The 10-day re-entry interval for stone fruits is considered feasible from an agronomic perspective.

Conclusions

For Headline EC fungicide, margins of exposure for mixer/loader/applicators are acceptable provided that the following label statement is adhered to: "The 6.5 L jug is intended for applicators who spray less than 130 ha (320 ac) per day. Applicators who spray more than 130 ha (320 acres) per day MUST use the 104 L totes." Margins of exposure for post-application exposure are acceptable with a re-entry interval of 48 hours. Therefore, registration of Headline EC Fungicide may be supported.

For Cabrio EG Fungicide, margins of exposure for mixer/loader/applicators are acceptable. With crop-specific re-entry intervals of 0–29 days, margins of exposure for post-application exposure are acceptable for bulb vegetables, cucurbit vegetables, fruiting vegetables, root vegetables, highbush blueberries, lowbush blueberries, strawberries and stone fruit. Registration for bulb vegetables, cucurbit vegetables, fruiting vegetables, root vegetables, highbush blueberries, lowbush blueberries, strawberries and stone fruits may be supported on the condition that an acceptable in vivo dermal absorption study be submitted.

4.0 Residues

4.1 Residue summary

The nature of the residue in potato, grape and wheat demonstrated that the metabolism of pyraclostrobin was label specific. The parent, pyraclostrobin, was the predominant residue in the chlorophenyl-labelled potato tubers, grapes, wheat grain, forage and straw, however, in the tolyl-labelled potato tubers and wheat grain, the major residue was the amino acid L-tryptophan formed from an anthranilic acid intermediate, via the shikimate pathway. The desmethoxy metabolite (BF 500-3) was also a significant component in grapes, potato tubers and wheat grain.

The lactating goat and laying hen metabolism studies indicated that pyraclostrobin was rapidly excreted, primarily as the unchanged parent compound, with minimal transfer to the tissues, milk and eggs (Appendix III, Table 1). Both pyraclostrobin and the desmethoxy metabolite BF 500-3 accounted for the majority of the residues in tissues, fat, milk and eggs. However, in the chlorophenyl label goat liver sample, the predominant metabolite was BF 500-5, resulting from the acid hydrolysis of pyraclostrobin, while in the hen liver sample, the glucose conjugate of the desmethoxy metabolite (500M32) accounted for the majority of the total radioactive residues (TRRs). An overall comparison of the metabolites identified in goat, hen and rat demonstrated that the metabolism of pyraclostrobin in all three species proceeds via the same major metabolic pathways.

The metabolic profiles in plant and animal suggest three pathways: hydrolysis of the N-methoxy group of the tolyl moiety yielding the desmethoxy metabolite BF 500-3, methoxylation or hydroxylation of the chlorophenyl, pyrazole and(or) tolyl rings, followed by glucose conjugation and cleavage of the ether linkage. Based on these studies, the residue of concern (ROC) in plant matrices was defined as the parent compound, pyraclostrobin and the desmethoxy metabolite, BF 500-3, while the ROC in animal matrices was defined as the parent compound, pyraclostrobin and the metabolites convertible to BF 500-5 (1-(4-chlorophenyl)-1H-pyrazol-3-ol) and BF 500-8 (1-(4-chloro-2-hydroxyphenyl)-1H-pyrazol-3-ol) for ruminant matrices and BF 500-5 and BF 500-9 (1-(3-chloro-4-hydroxyphenyl)-1H-pyrazol-3-ol) for poultry matrices.

The confined crop rotation study demonstrated that the metabolism of pyraclostrobin in rotated crops (wheat, lettuce and radish), planted in treated soil, was similar to that in primary crops with pyraclostrobin undergoing demethoxylation, followed by further degradation to medium and polar metabolites, conjugation and incorporation into natural products such as starch, cellulose and(or) lignins. The study supports the definition of the residue of concern (ROC), pyraclostrobin and the desmethoxy metabolite BF 500-3, as defined in the plant metabolism studies.

Two analytical methods, LC/MS/MS Method D9808 and HPLC/UV Method D9904, were submitted for the determination of the ROC in plant matrices. While both methods were proposed for enforcement, only the LC/MS/MS Method D9808 was used for data gathering. The method limits of quantitation (LOQs) for pyraclostrobin and BF 500-3 were the same for both methods: 0.02 ppm/analyte. Good linearity (correlation coefficient, $r > 0.999$), was observed in the range of 0.5–20 ng/µL for pyraclostrobin and BF 500-3. The interlaboratory validation (ILV) demonstrated good reliability and reproducibility of the LC/MS/MS Method D9808 and HPLC/UV Method D9904 for the determination of residues of pyraclostrobin and BF 500-3 in plant matrices. The standard deviations measured with respect to recoveries following spiking at the LOQ, did not exceed 20%, indicative of the method having good repeatability. Representative chromatograms of control samples showed no peaks above the chromatographic background. The spike sample chromatograms from Method D9808 contained only the analyte peaks at spiking levels of 0.02 ppm and 2.0 ppm while in Method D9904, the peaks at spiking levels of 2.0 ppm were better defined and symmetrical than those from spiking at 0.02 ppm. Overall, the LC/MS/MS Method D9808 is the preferred enforcement method as it specifically identifies the ROC.

For animal matrices, three analytical methods were submitted for data gathering and enforcement purposes. The HPLC/UV Method 439/0 used to quantitate residues of pyraclostrobin alone in livestock matrices. Method 446 was initially developed using GC/MS Method 446/0 in milk but was replaced with the shorter duration LC/MS/MS Method 446/1 for ruminant commodities. This method is a common moiety method used to determine residues of the parent and the metabolites hydrolyzable to BF 500-5 and BF 500-8. For this method, residues of pyraclostrobin and BF 500-3 (ROC) are hydrolyzable to BF 500-5 while metabolites which contain a hydroxy group at the 2 position of the chlorophenyl ring would be hydrolyzable to BF 500-8. The LC/MS/MS Method D9902 is a common moiety method developed to analyze residues of the parent and the metabolites hydrolyzable to BF 500-5 and BF 500-9 in poultry commodities.

For the HPLC Method 439/0, the method limits of quantitation (LOQs) for pyraclostrobin were 0.01 ppm for milk and 0.05 ppm for eggs and tissues. Good linearity (correlation coefficient, r>0.99), was observed in the range of 1.25–20 ng for pyraclostrobin. The interlaboratory validation (ILV) demonstrated good reliability and reproducibility of the HPLC/UV Method 439/0 for the determination of residues of pyraclostrobin in milk and tissues. The standard deviations measured with respect to recoveries following spiking at the LOQ were within 20%, indicative of the method having good repeatability.

For the LC/MS/MS common moiety method 446/1, the LOQs for BF 500-5 and BF 500-8 were each 0.01 ppm for milk and 0.05 ppm for tissues. When incorporating a dilution of the liver sample, the interlaboratory validation obtained acceptable recoveries of pyraclostrobin and BF 500-10. Therefore, the LC/MS/MS Method 446/1 was deemed to be reliable and reproducible. The standard deviations measured with respect to recoveries following spiking of pyraclostrobin and BF 500-10 ((Methyl N-[2-((1-(4-chloro-2-hydroxyphenyl)-1H-pyrazol-3-yl)oxymethyl)phenyl] N-methoxy carbamate)—representative of metabolites hydrolyzable to BF 500-8) at the LOQ did not exceed 20%, indicative of the method having good repeatability. The control chromatograms generally had no peaks above the chromatographic background and the spiked sample chromatograms contained only the analyte peak.

For the poultry-specific analytical method D9902, the LOQ was reported to be 0.05 ppm/analyte in eggs and tissues. The method/detector response was linear within the range of 25–250 pg for both BF 500-5 and BF 500-9 (correlation coefficient r>0.996). An ILV was not conducted, on the basis that this method was very similar to the LC/MS/MS Method 446/1. However, given the difficulties encountered in the ILV for Method 446/1 and the requirement to establish MRLs for pyraclostrobin in/on poultry matrices, an ILV should be submitted for this method. The relative standard deviations measured with respect to recoveries following spiking of pyraclostrobin and BF500-16 ((Methyl N-[2-((1-(3-chloro-4-hydroxyphenyl)-1H-pyrazol-3-yl)oxymethyl)phenyl] N-methoxy carbamate)—representative of metabolites hydrolyzable to BF 500-9) at the method LOQs were greater than 20% for pyraclostrobin in/on liver but were deemed acceptable for both analytes in all the remaining matrices. Due to peak shouldering, the analyte peak was not totally symmetrical.

Submitted freezer storage stability studies indicated that residues of pyraclostrobin and the desmethoxy metabolite BF 500-3 were stable for at least 19 months when stored at -10°C in/on spiked samples of peanut nutmeat, processed oil, grape juice, sugar beet tops and roots, tomatoes, wheat grain and straw.

The interim storage stability data indicated that residues of pyraclostrobin and the metabolite BF 500-10 are stable under frozen storage conditions (-20°C) in/on spiked samples of cow milk, liver and muscle for up to 90 days (~3 months). However, milk and tissue samples collected from the dairy cattle feeding study were stored frozen from collection to analysis for up to three months for whole and skim milk and greater than three months for the remaining commodities. Therefore, the submitted storage stability data are adequate to support the storage conditions and intervals of the whole and skim milk samples, however, additional storage stability data will be required to support the storage conditions and intervals of the milk fat and tissue samples from the ruminant feeding study.

For poultry matrices, the storage stability data indicated that residues of pyraclostrobin and the metabolite BF 500-16 were stable under frozen storage conditions (<-10°C) in/on spiked samples of eggs for up to seven months. Samples collected from the poultry feeding study were stored frozen from collection until analysis for up to five months for eggs, four months for fat, three months for liver and six months for muscle. The submitted storage stability data for eggs are adequate to support the storage conditions and intervals of the egg samples from the poultry feeding study. The petitioner has referenced the ruminant storage stability data to support the storage conditions and intervals of the remaining poultry matrices. The storage stability data for ruminant commodities can be translated to poultry commodities. Therefore, additional storage stability data are required to support the storage conditions and intervals of the milk fat, ruminant and poultry tissue samples.

Supervised residue trials were conducted on the representative crops of the following crop subgroups/groups: Root vegetables (except sugar beet), Tuberous and Corm Vegetables, Bulb Vegetables, Dried Shelled Pea and Bean (except Soybean), Fruiting Vegetables (Except Cucurbits), Cucurbit Vegetables, Citrus Fruits, Stone Fruits, Berries, Tree Nuts, Pistachio, Cereal Grains, Banana, Grape, Peanut and Strawberry. Several of these trials were neither conducted according to the proposed GAP (good agricultural practice) nor in the required growing regions (as per Regulatory Directive DIR98-02), therefore, additional supervised residue trials will be required to support their uses. The commodities for which the uses were supported were: Root and Tuber Vegetables (Except Sugar Beets) Crop Subgroup 1B, Tuberous and Corm Vegetables Crop Subgroup 1C, sugar beets, Fruiting Vegetables Crop Group 8, cereal grains (barley, rye and wheat) and strawberries including all the imported crops/crop groups: Citrus Fruits Crop Group 10, Tree Nut Crop Group 14, banana, pistachios and peanuts. All remaining uses, Bulb Vegetables Crop Group 3, Dried Shelled Pea and Bean (Except Soybean) Crop Subgroup 6C, Cucurbit Vegetables Crop Group 9, Stone Fruits Crop Group 12, Berries Crop Group 13 were supported on a temporary basis pending the submission of additional supervised residue trials conducted at GAP in the representative growing regions.

The processing studies, conducted on citrus fruits, grapes, peanuts, plums, sugar beets, tomato and wheat, demonstrated that there was a slight concentration of residues of pyraclostrobin and the desmethoxy metabolite BF 500-3 in citrus oil, raisins, peanut oil, prunes and tomato paste. No concentration was observed in any other processed fraction.

Maximum combined residues of pyraclostrobin and the metabolites hydrolyzable to BF 500-5 and BF 500-8 were <0.02–0.175 ppm in whole milk, 0.0393–0.102 ppm in skim milk, 0.131–0.258 ppm in milk fat, 2.06–2.78 ppm in liver, 0.396 ppm in kidney and <0.1 ppm in both fat and muscle when cattle were administered the highest dose of 89.6 ppm, corresponding to 2.5× the maximum theoretical dietary burden (MTDB). Consequently, when exposed to feed treated according to the proposed label rate, total pyraclostrobin residues in fat, meat and milk are not expected to exceed 0.1 ppm while in meat by-products (except liver), total residues will be below 0.2 ppm. The anticipated liver residues resulting from the feeding of GAP treated crops are 1.5 ppm.

At the feeding level of 3.01 ppm (equivalent to 8.6× the MTDB), combined residues of pyraclostrobin and the metabolites hydrolyzable to BF 500-5 and BF 500-9 in all poultry tissues and eggs were less than the method LOQ of 0.05 ppm. Following exposure to feed treated according to the proposed label, total residues of pyraclostrobin in eggs and poultry tissues are not expected to exceed the method LOQ (0.05 ppm). Therefore, MRLs for poultry matrices will not be established.

The Dietary Exposure Evaluation Model™ (DEEM™) software which used data from the USDA 1994–98 Continuing Survey of Food Intakes by Individuals (CSFII) was used to assess the potential chronic dietary exposure to total residues of pyraclostrobin resulting from the proposed uses on various field crops, fruits and vegetables. The assessment was carried out using proposed Canadian maximum residue limits (MRLs) and MRLs proposed for imported crops. An EEC value for drinking water was also included in the assessment. It was estimated that the chronic dietary exposure to pyraclostrobin from food and water represented approximately 35% of the interim ADI (0.003 mg/kg bw) for children 1–6 years old. The PDI for the remaining population subgroups, including infants, children, adults and seniors, each represented <29% of the interim ADI.

Consequently, the consumption estimates coupled with the recommended MRLs indicate that there is adequate protection of the consumer, including infants, children, adults and seniors, from exposure to dietary residues of pyraclostrobin.

5.0 Fate and behaviour in the environment

5.1 Physical and chemical properties relevant to the environment

Pyraclostrobin has low solubility in water over the range of pH 4 to pH 9 (2.41–1.9 mg a.i./L). This is one of the indicators of a low potential for leaching (Table 2). The vapour pressure of pyraclostrobin is 2.6×10^{-8} Pa at 20°C, and Henry's Law constant is 4.13×10^{-11} atm. m^3/mole. These values indicate that pyraclostrobin is non-volatile under field conditions and from water and moist soil surfaces. The log K_{ow} is 4.2 at pH 6.5 and 3.8 at pH 6.2, indicating a potential for pyraclostrobin to bioaccumulate. Pyraclostrobin does not have any dissociable moiety and therefore, does not dissociate in water. The maximum light absorption was at 275 nm, indicating minimal direct phototransformation in the environment

5.2 Abiotic transformation

Hydrolysis of pyraclostrobin was minimal during the 30-day study period. Therefore, it is not considered to be an important route of transformation in the environment. The minor transformation products identified in the hydrolysis study were BF 500-5, BF 500-6, and BF 500-7; all formed at a maximum of 4% of the applied.

Phototransformation of pyraclostrobin on soil indicated that the first-order half-lives of BAS 500 F in soil at 40% MWHC were 24–41 day and 33–44 day for the dark and irradiated samples, respectively. Therefore, phototransformation of pyraclostrobin on soil is not an important route of transformation. No new transformation products were formed in the irradiated samples. BF 500-3, BF 500-6 and BF 500-7 were formed as minor transformation products in irradiated and dark samples. Phototransformation of pyraclostrobin in aqueous solution occurred with a first-order half-life of less than 2 hours. No transformation was reported to occur in the dark samples. The major transformation products detected were 500M78, 500M76 (BF 500-14), 500M58, 500M62 (BF 500-13), and 500M60 (BF 500-11). All were transient and the concentrations were below 10% of the applied at the end of the study, except BF 500-11 (37% of the applied). In the irradiated samples, at the end of the study, 22% and 4% of the applied radioactivity was present as $^{14}CO_2$ in the chlorophenyl and tolyl label samples, respectively. Therefore, photolysis of pyraclostrobin in aqueous buffer at pH 5 under Xenon lamp (with emission wavelength of 290–800 nm) indicated that indirect photolysis may be an important pathway of transformation. In the natural environment, several dissolved organic and inorganic constituents could act as photosensitizers and cause indirect photolysis.

5.3 Biotransformation

Pyraclostrobin was moderately persistent to persistent under aerobic soil conditions with a first-order half-life of 82–277 day. The DT_{50} ranged from 14 to 270 day. In some soils, the aerobic biotransformation was biphasic with a relatively rapid rate occurring during the initial period, and a subsequent gradual deceleration. The major transformation products detected included BF 500-3 and BF 500-6 (both formed at a maximum of 18% of the applied). The minor transformation product detected were BF 500-5 and BF 500-7. Under anaerobic soil conditions, pyraclostrobin is non-persistent with a half-life of 3 days. The major transformation products formed under anaerobic soil included BF 500-3 and BF 500-4. The minor transformation product was BF 500-5. Please note that no acceptable studies on the aerobic biotransformation of pyraclostrobin in water-sediment systems were submitted (the sediment was anaerobic).

5.4 Mobility

The adsorption/desorption studies indicated that pyraclostrobin will be immobile in soil (sand, loamy sand, and sandy loam), BF 500-3 will be slightly mobile to immobile and BF 500-5 will be of low to moderate mobility in soil. This indicates that the parent and BF 500-3 have low potential for leaching, and BF 500-5 has low to moderate potential for leaching. The low potential mobility of the parent was also supported by the low solubility of pyraclostrobin in water.

5.5 Dissipation and accumulation under field conditions

Laboratory studies of biotransformation indicated that pyraclostrobin is moderately persistent to persistent in aerobic soil with the formation of BF 500-6 and BF 500-3 as the major transformation products identified. In the field, dissipation of pyraclostrobin followed a biphasic pattern. The dissipation rate was initially fast, followed by a gradual deceleration. The DT_{50} values at the Canadian sites (Alberta, Manitoba, Ontario and P.E.I.) were 15–48 day. The DT_{75} values were 40–320 day, and the DT_{90} values were 110 day to more than one year. The DT_{50} values at the Canadian equivalent U.S. sites (South Dakota, North Dakota, New York) were 11–21 day. The DT_{75} and DT_{90} values in these U.S. sites were 30–100 day and 100–320 day, respectively. Based solely on the DT_{50} values, pyraclostrobin would be classified as non-persistent to moderately persistent under Canadian field conditions. The DT_{75} and DT_{90} values, however, indicate much greater persistence of pyraclostrobin than do the DT_{50} values. With the application of pyraclostrobin in late July to early August, the carry-over of the parent at the end of the growing season (late October–early November) was 14% of the applied at the Ontario site and 35% of the applied at the Alberta site. The corresponding values at the Manitoba and PEI sites were 34–37% of the applied. The carry-over of pyraclostrobin after one full year in Ontario, Alberta, Manitoba and PEI were 4, 15, 18 and 10% of the applied, respectively, which is just below the level of concern. BF 500-6 was the only major transformation product detected in Canadian relevant sites. On the other hand, BF 500-3, BF 500-5, BF 500-6, and BF 500-7 were detected as minor transformation products. This indicated that the transformation of pyraclostrobin was a dissipation route under terrestrial field conditions. At all sites, the parent and the transformation products were detected primarily in the top 0–15 cm soil depth. This indicated that the residues were relatively immobile, and leaching was not an important route of dissipation under field conditions. Adsorption-desorption studies also indicated the immobility of pyraclostrobin in soil with low potential for leaching. There was good agreement between laboratory and field studies on persistence and mobility/leaching. Similar dissipation times were obtained for the EC and WG formulations at a U.S. site.

5.6 Bioaccumulation

The log K_{ow} of pyraclostrobin at pH 6.5 is 4.2, which indicates a potential for bioaccumulation. Bioaccumulation of pyraclostrobin (chlorophenyl and tolyl label) was studied in bluegill sunfish under flow-through conditions. Dilution water in aquaria was treated with [^{14}C]Pyraclostrobin at a nominal concentration of 300 ng equivalent/L. The accumulation phase was carried out for 37 days, followed by a 14- (chlorophenyl label study) or 21-day (tolyl label study) depuration period. All radioactivity in the water was present as the parent.

The concentration of total radioactivity in fish tissues reached steady state within 2.3–3.2 days. Pyraclostrobin was the primary radioactive component recovered from the edible and non-edible fish tissues. Bioconcentration factors were 232–269× for the edible, 1171–1246× for the non-edible, and 675–736× for the whole fish tissues. However, depuration was rapid with elimination of 50% of the total [^{14}C]residues accumulated during 35 days of exposure, by day 1 of the depuration period and >90% of the accumulated residues in the following 2–3 days of depuration. Because of the rapid depuration of pyraclostrobin, bioaccumulation is not expected to be a concern.

5.7 Summary of fate and behaviour in the terrestrial environment

Laboratory studies of transformation in soil indicated that biotransformation is the major pyraclostrobin transformation route in aerobic soil as compared to hydrolysis and phototransformation (Appendix IV, Table 1). Hydrolysis of pyraclostrobin was minimal during the 30-d study period. The minor hydrolysis products identified were BF 500-5, BF 500-6 and BF 500-7. Phototransformation of pyraclostrobin on soil indicated that the first-order half-lives in soil were 24–41 day and 33–44 day for the dark and irradiated samples, respectively. Therefore, phototransformation on soil is not an important route of transformation. Based on the biotransformation half-life, pyraclostrobin was moderately persistent to persistent in aerobic soil, with the formation of BF 500-3 and BF500-6 as the major transformation products. In the field, dissipation of pyraclostrobin followed a biphasic pattern. The dissipation rate was initially fast, followed by a gradual deceleration. The DT_{50} values at the Canadian sites were 15–48 day. The DT_{75} values were 40–320 day, and the DT_{90} values were 110 day to more than one year. The DT_{50} values at the Canadian equivalent U.S. sites (South Dakota, North Dakota, New York) were 11–21 day. The DT_{75} and DT_{90} values in these U.S. sites were 30–100 day and 100–320 day, respectively. Based solely on the DT_{50} values, pyraclostrobin would be classified as non-persistent to moderately persistent under Canadian field conditions. The DT_{75} and DT_{90} values, however, indicate much greater persistence of pyraclostrobin than do the DT_{50} values. The carry-over of pyraclostrobin after one full year in Ontario, Alberta, Manitoba and PEI were 4, 15, 18 and 10% of the applied, respectively, which is just below the level of concern. BF 500-6 was the only major transformation product detected in Canadian relevant sites. On the other hand, BF 500-3, BF 500-5, BF 500-6, and BF 500-7 were detected as minor transformation products. This indicated that the transformation of pyraclostrobin was a dissipation route under terrestrial field conditions. At all sites, the parent and the transformation products were detected primarily in the top 0–15 cm soil depth. This indicated that the residues were relatively immobile, and leaching was not an important route of dissipation under field conditions. Laboratory adsorption-desorption studies also indicated the immobility of pyraclostrobin in soil with low potential leaching. Similar field dissipation times were obtained for the EC and WG formulations at a U.S. site.

5.8 Summary of fate and behaviour in the aquatic environment

Hydrolysis of pyraclostrobin is not an important route of transformation in the aquatic environment (Appendix IV, Table 2). Indirect photolysis may be an important route of transformation in water. The aqueous photolysis half-life is approximately 2 h with the formation of BF 500-11, BF 500-13, BF 500-14, 500M78, and 500M58 as the major transformation products. All these major transformation products were transient and the concentrations were below 10% of the applied at the end of the study, except BF 500-11 (37% of the applied). No acceptable studies were submitted to determine the biotransformation of pyraclostrobin in aerobic water. Owing to the design of the submitted study, it was not possible to assess the aquatic biotransformation under strictly aerobic conditions. Therefore, an additional study is required to assess the biotransformation of pyraclostrobin in aerobic water-sediment system.

5.9 Expected environmental concentrations

5.9.1 Soil

As the rates and the proposed crops are different for Headline EC and Cabrio EG, the expected environmental concentration (EEC) of pyraclostrobin in soil was calculated separately, based on their maximum application rate, number of applications, intervals between applications, and the aerobic soil biotransformation half-life (277 day).

Headline EC: The maximum rate of application of Headline EC is for potatoes (1350 g a.i./ha per season). It is applied at 225 g a.i./ha, six times at 5-day intervals. NAQoI (North American Quinone outside Inhibitors, a North American Fungicide Resistance Action Committee (FRAC) for the QoI = strobilurin fungicides), however, recommends a maximum of two sequential sprays of Headline EC, followed by at least two sprays of fungicide(s) with a different mode of action. When the half-life of pyraclostrobin, the interval based on the NaQoI recommendation, and the number of applications are considered, the maximum cumulative application rate of Headline EC in soil is 1277.2 g a.i./ha. The EEC of pyraclostrobin in soil (15 cm soil depth) using this cumulative application rate is 0.57 mg a.i./kg soil based on a bulk density of 1.5 g/cm3.

Cabrio EG: The maximum rate of application of Cabrio EG is for fruiting vegetables (1200 g a.i./ha per season). It is applied at 200 g a.i./ha, six times at 7-day intervals. NAQoI, however, recommends a maximum of two sequential sprays of Cabrio EG, followed by at least two sprays of fungicide(s) with a different mode of action. When the half-life of pyraclostrobin, the interval based on the NaQoI recommendation, and the number of applications are considered, the maximum cumulative application rate of Cabrio EG in soil is 1110.9 g a.i./ha. The EEC of pyraclostrobin in soil (15 cm soil depth) using this cumulative application rate is 0.49 mg a.i./kg soil based on a bulk density of 1.5 g/cm^3.

5.9.2 Aquatic systems

Drinking water
Pyraclostrobin residues in potential drinking water sources (ground water and surface water) at the Level 1 (Screening Level) were modelled. The maximum drinking water concentration of pyraclostrobin in ground-water source as a result of leaching was estimated using the model LEACHM (maximum annual peak over 20 years; Table 4). Drinking water concentrations in surface water sources (reservoir and dugouts) as a result of surface run-off were estimated using the linked PRZM/EXAMS models (90th percentile of the yearly peak and yearly average over 50–75 years; Table 4). These values are considered to be "upper bound" concentrations in a drinking water source.

Table 4 The estimated environmental concentrations (Level 1) of pyraclostrobin in drinking water sources

Groundwater (µg ai/L)	**Reservoir (µg a.i./L)**		**Dugout (µg a.i./L)**	
Annual Average Concentration[1]	Acute[2]	Chronic[3]	Acute[2]	Chronic[3]
1.2	11.4	1.7	13.7	0.44

[1] Maximum yearly average for a 20-year simulation
[2] 90th percentile of yearly peaks
[3] 90th percentile of yearly averages

Direct over-spray in surface water
As there was no acceptable aerobic water or water-sediment (biotransformation) study, the maximum seasonal application rate is used to calculate the EEC of pyraclostrobin from direct over-spray in surface waters at 30 cm water depth. The EEC in water after the application of Headline EC at the maximum seasonal rate (1350 g a.i./ha) was 0.45 mg a.i./L. The EEC in water after the application of Cabrio EG at the maximum seasonal rate (1200 g a.i./ha) was 0.40 mg a.i./L.

5.9.3 Vegetation and other food sources

The EECs in vegetation and food sources are calculated based on the maximum annual label rate of application of Headline EC (1350 g a.i./ha) and Cabrio EG (1200 g a.i./ha). This did not account for any transformation of pyraclostrobin on the foliage (as data were not available). Direct over-spray scenario using a nomogram developed by the U.S. EPA from the data of Hoerger and Kenaga (1972), Kenaga (1973), and modified according to

Fletcher et al. (1994) for use in ecological risk assessment (Urban and Cook, 1986) was used (Appendix IV, Tables 3–5).

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

Pyraclostrobin was relatively non-toxic to honey bees on a contact basis (Appendix IV, Table 6). Several studies were conducted to determine the effects of BAS 500 00F (247.8 g a.i./L; EC) on predatory mites (Acari: *Phytoseiidae*), parasitic wasps (*Aphidius rhopalosiphi*), foliage dwelling predators (lady bird beetle: *Coccinella septempunctata*; green lacewing: *Chrysoperla carnea*), and soil-dwelling insects (carabid beetle: *Poecilus cupreus*; wolf spiders: *Pardosa sp.*). Based on the field/greenhouse study, BAS 500 00F is classified as harmless to low risk to predatory mites (at a dose of 160–640 g a.i./ha), and parasitic wasps (at a dose of 320 g a.i/ha) according to the BBA hazard rating classification. The laboratory studies, however, indicated that BAS 500 00F was classified as moderately harmful to populations of predatory mites and parasitic wasps (both exposed at 320 g a.i/ha). The rating used in these studies depends on the magnitude of the overall effect (E), and classifies the test substance as follows: <30%—harmless; 31–80%—slightly harmful; 81–99%—moderately harmful; >99%—extremely harmful. In laboratory studies, BAS 500 00F (320 g a.i./ha) was found to be highly toxic to lady bird beetle, harmless to slightly harmful to green lacewing. BAS 500 00F is considered to be harmless to soil dwellers like carabid beetle and wolf spiders when applied at 320 g a.i./ha. According to the EPA classification, pyraclostrobin was practically non-toxic to bobwhite quail and mallard duck. In the reproductive toxicity studies, the NOAEC was 1062 mg a.i/kg dw for bobwhite quail and mallard duck. The effects on mammals are given in Section 3.1.

6.2 Effects on aquatic organisms

Pyraclostrobin is very highly toxic to daphnids, rainbow trout, bluegill sunfish, mysid shrimps, and sheepshead minnow (Appendix IV, Table 7). The mollusk shell deposition study also indicated that pyraclostrobin is very highly toxic. The acute studies on BF 500-11, BF 500-13, and BF 500-14 indicated that these transformation products were practically non-toxic to slightly toxic to daphnids and rainbow trouts. The most sensitive aquatic toxicity endpoint was the 120-h NOEC (1.18 μg a.i./L) for freshwater diatoms.

6.3 Effects on biological methods of sewage treatment

Not applicable.

6.4 Risk characterization

6.4.1 Environmental behaviour

Laboratory studies of transformation in soil indicated that pyraclostrobin is moderately persistent to persistent in aerobic soil with the formation of BF 500-3 and BF 500-6 as the major transformation products. Hydrolysis and phototransformation of pyraclostrobin in soil are not important routes of transformation. The minor hydrolysis products identified were BF 500-5, BF 500-6 and BF 500-7. Phototransformation of pyraclostrobin on soil indicated that the first-order half-lives in soil are 24–41 d and 33–44 d for the dark and irradiated samples, respectively. Pyraclostrobin is non-persistent in anaerobic soil with the formation of BF 500-3, BF 500-4 and 500M75 as the major transformation products. The adsorption-desorption studies indicated that pyraclostrobin is immobile in soil, and BF 500-3 is slightly mobile to immobile. BF 500-5 has low to moderate mobility. In the field, dissipation of pyraclostrobin followed a biphasic pattern. The dissipation rate was fast initially, followed by a gradual deceleration. The DT_{50} values at the Canadian sites were 15–48 d. The DT_{75} values were 40–320 d, and the DT_{90} values were 110 d to more than one year. Based solely on the DT_{50} values, pyraclostrobin would be classified as non-persistent to moderately persistent under Canadian field conditions. The DT_{75} and DT_{90} values, however, indicate much greater persistence of pyraclostrobin than do the DT_{50} values. The carry-over of pyraclostrobin after one full year in Canadian sites is just below the level of concern. BF 500-6 was the only major transformation product detected in relevant Canadian sites. On the other hand, BF 500-3, BF 500-5, BF 500-6, and BF 500-7 were detected as minor transformation products. This indicated that the transformation of pyraclostrobin was a dissipation route under terrestrial field conditions. At all sites, the parent and the transformation products were detected primarily in the top 0–15 cm soil depth. This indicated that the residues were relatively immobile, and leaching was not an important route of dissipation under field conditions.

Hydrolysis of pyraclostrobin is not an important route of transformation in the aquatic environment. Indirect photolysis may be an important route of transformation in water. The aqueous photolysis half-life is approximately 2 h with the formation of BF 500-11, BF 500-13, BF 500-14, 500M78, and 500M58 as the major transformation products. All these major transformation products were transient and the concentrations were below 10% of the applied, at the end of the study, except BF 500-11. No acceptable studies were submitted to determine the biotransformation of pyraclostrobin in aerobic water.

6.4.2 Terrestrial organisms

As different rates were recommended for Headline EC and Cabrio EG, the risk characterization was done separately for these products (Appendix IV, Tables 8 and 9).

Headline EC

Wild birds: Wild birds, such as bobwhite quail and mallard duck, could be exposed to pyraclostrobin residues as a result of consumption of sprayed vegetation, contaminated prey or spray drift. The bobwhite diet consists of approximately 30% small insects, 15% forage crops and 55% grain and seeds. The EEC of pyraclostrobin in the bobwhite diet after the application of Headline EC, based on the maximum application rate (1350 kg a.i./ha) is 236 mg a.i./kg dw diet. The mallard duck diet consists of approximately 30% large insects and 70% grain and seeds. Therefore, the EEC in mallard diet is 46 mg a.i./kg dw diet (Appendix IV, Tables 3 and 5).

In the acute oral toxicity study, the mean body weight per individual (BWI) of bobwhite quail in the control treatment was 0.195 kg bw/individual, while the mean food consumption (FC) was 0.018 kg dw of diet/individual/d. The daily intake (DI=FC*EEC) was, therefore, 4.26 mg a.i/individual/d. The reported LD_{50} and NOEL values were >2000 and 500 g a.i/kg bw, respectively. When expressed on a per individual basis, the $LD_{50(individual)}$ (=LD_{50}*BWI) was 390 mg a.i/individual, and the $NOEL_{(individual)}$ (=NOEL*BWI) was 97.5 mg a.i/individual. Based on the DI and the $LD_{50(individual)}$, it would take a bobwhite quail 92 continuous days of feeding to attain the dose equivalent to that administered in the laboratory by gavage, that killed 50% of the laboratory population. Similarly, based on the DI and the $NOEL_{(individual)}$, the maximum number of days of continuous intake by a bobwhite, to attain a dose equivalent to the dose administered by gavage, that had no observable effect on the laboratory population was 23 d. Therefore, pyraclostrobin does not present an acute risk to the bobwhite quail at the proposed application rate of Headline EC.

Dietary studies with both the bobwhite quail and the mallard duck indicated that the NOECs (2500 and 625 mg a.i/kg dw of diet, respectively) were greater than the EECs for each species. The margin of safety (MOS = NOEC/EEC) were 11 and 14, respectively. The reproductive studies in bobwhite quail and mallard indicated a NOEC of 1062 mg a.i/kg dw of diet. The MOS based on the reproductive parameters is 5 for bobwhite quail and 23 for mallard ducks. Pyraclostrobin will pose only negligible dietary or reproductive risks to birds when Headline EC is applied at a maximum rate.

Wild mammals: Wild mammals such as rats, mice, and rabbits could be exposed to pyraclostrobin residues as a result of consumption of sprayed vegetation and(or) contaminated prey. The rat diet consists of approximately 70% short grass, 20% grain/seed and 10% large insects. Therefore, the EEC in the rat diet is 681 mg a.i./kg diet. Based on the DI and the $LD_{50(individual)}$, it would take a rat 43 continuous days of feeding to attain the dose equivalent to that administered in the laboratory by gavage that killed 50% of the laboratory population. Therefore, pyraclostrobin does not present an acute risk to rats. The 90-day dietary toxicity studies in rat indicate that the NOAEL (50 mg a.i./kg diet) is lower than the EEC in the diet (681 mg a.i./kg diet). The MOS is 0.07. Also, the reproductive NOAEL in rats was 300 mg a.i./kg bw, which is lower than the EEC in the rat diet (MOS = 0.44). Therefore, there are potential dietary and reproductive risks to the rat from the application of Headline EC at the maximum application rate, if rats consume contaminated food continuously for 90 days. The mouse diet consists of approximately 25% short grass, 50% grain/seed and 25% leaf and leafy crops. Therefore, the EEC in the mouse diet is 677 mg a.i./kg diet. The 90-day dietary toxicity studies in mice indicated that the NOAEL (50 mg a.i./kg diet) is lower than the EEC in the diet (677 mg a.i./kg diet). Therefore, there is a potential dietary risk to mice from the application of Headline EC at the maximum application rate, if mice consume contaminated food continuously for 90 days.

Honeybee: Pyraclostrobin is not toxic to bees on an acute contact basis. The NOEC was > 100 μg a.i./bee (112 kg a.i./ha). The margin of safety (MOS = NOEC/EEC) is 83 (Appendix IV, Table 8). Therefore, application of pyraclostrobin will pose only negligible risk to bees on an acute contact basis when Headline EC is applied at the label rates.

Earthworms: As the maximum EEC of pyraclostrobin in soil is 0.57 mg a.i./kg soil, and the NOEC for earthworms is 151 mg a.i./kg substrate, pyraclostrobin will pose only negligible risk to earthworms at the proposed use rates. The MOS is 265.

Other beneficial insects: Several field and laboratory studies were carried out (in Germany and Switzerland) to determine the effects of BAS 500 00F (250 g a.i./L). Most of the studies, however, were carried out with only one concentration. According to the BBA classification, BAS 500 00F (250 g a.i./L) applied at160–640 g a.i./ha is harmless to low risk to predatory mites. No harmful effects were observed in soil dwellers (wolf spiders and carabid beetles) when BAS 500 00F was applied at 320 g a.i./ha. At this rate under laboratory conditions, pyraclostrobin was highly toxic to lady bird beetles and was found to be harmless to green lacewing. The highest rate of application of Headline EC is 225 g a.i/ha, which was lower than the test dose. Therefore, it is possible that, under field conditions, the risk to beneficial insects will be low.

Vascular plants: As the studies on terrestrial plants were conducted with rates (132 g a.i./ha) lower than the proposed maximum rate of application (225 g a.i./ha), the risk assessment could not be conducted at this time.

Cabrio EG

The EEC of pyraclostrobin is 210 mg a.i./kg dw in the bobwhite quail diet and 41 mg a.i./kg dw in the mallard duck diet when Cabrio EG (Appendix IV, Tables 4 and 5) is applied at the maximum rate (1200 g a.i./ha). Based on the DI and $\text{NOEL}_{\text{(individual)}}$, it would take a bobwhite quail 26 d of continuous feeding to attain the dose equivalent to that administered by gavage that has no-observable effect on the laboratory population. Therefore, pyraclostrobin does not present an acute risk to bobwhite quail at the proposed application of Cabrio EG. In addition, application of Cabrio EG at the maximum rate will pose only negligible dietary or reproductive risks to birds.

The EEC of pyraclostrobin in the rat diet after the application of Cabrio EG at the maximum rate is 605 mg a.i./kg dw and that in the mouse diet is 602 mg a.i./kg dw. Based on the DI and $\text{NOEL}_{(\text{individual})}$, it would take a rat 48 d of continuous feeding to attain the dose equivalent to that administered by gavage, that killed 50% of the laboratory population. Therefore, pyraclostrobin does not present an acute risk to rats at the proposed application rate of Cabrio EG. There is a high potential dietary risk to rats (MOS = 0.058) and mice (MOS = 0.015) from the application of Cabrio EG at the maximum application rate, if they consume contaminated food continuously for 90 days. The reproductive risks to rat (MOS = 0.008) are also high.

Honeybee/earthworms: Pyraclostrobin will pose only negligible risk to bees on an acute contact basis (MOS = 93) and to earthworms (MOS = 264) when Cabrio EG is applied at the label rates (Appendix IV, Table 9).

Other beneficial insects: The highest rate of application of Cabrio EG is 224 g a.i/ha. Therefore, it is possible that under field conditions, the risk to beneficial insects will be low when Cabrio EG is applied.

Vascular plants: As the studies on terrestrial plants were conducted with rates (132 g a.i./ha) lower than the proposed maximum rate of application (200 g a.i./ha), the risk assessment could not be conducted at this time.

6.4.3 Aquatic organisms

Headline EC

Non-target freshwater invertebrates: The most sensitive endpoint was the chronic NOEC (4 µg a.i./L) based on the reproduction and growth of offspring of *Daphnia sps*. The EEC in water after the application of Headline EC was 0.45 mg a.i./L. Therefore, there is very high risk to fresh water invertebrates at the proposed maximum application rate of Headline EC. The MOS is 0.009 (Appendix IV, Table 8).

Fish: The most sensitive endpoint was the chronic NOEC for rainbow trout (2.35 µg a.i./L). Based on the EEC, there is very high potential risk to fish at the proposed maximum application rate of Headline EC. The MOS is 0.005.

Aquatic plants: The most sensitive endpoint for the fresh water aquatic plants is the 120-h NOEC based on biomass production of diatoms (1.18 µg a.i./L). This is also the most sensitive aquatic endpoint. The MOS is 0.003, based on the EEC of 0.45 mg a.i./L. Therefore, there is a very high potential risk to aquatic plants at the proposed maximum application rate of Headline EC.

Non-target marine organisms: The most sensitive marine invertebrate endpoint is the 96-h NOEC for mysid shrimps (2.12 µg a.i./L). The most sensitive endpoint for marine fish is the 36-d NOEC for fathead minnow (4.1 µg a.i./L). The most sensitive endpoint for the marine algae is the 120-h NOEC for marine diatoms (9.7 μg a.i./L). Based on the EEC of pyraclostrobin in water, there is a high to very high risk to marine invertebrates, fish and algae at the proposed maximum application rate of Headline EC. The MOS is 0.005 for mysids, 0.009 for fish, and 0.02 for diatoms.

Cabrio EG

Non-target freshwater invertebrates: The most sensitive endpoint was the chronic NOEC (4 μg a.i./L) based on the reproduction and growth of offspring (*Daphnia sps*). The EEC in water after the application of Cabrio EG at the highest rate was 0.40 mg a.i./L. Therefore, there is high risk to fresh water invertebrates at the proposed maximum application rate of Cabrio EG. The MOS is 0.03 (Appendix IV, Table 9).

Fish: The most sensitive endpoint was the chronic NOEC for rainbow trout (2.35 μg a.i./L). Based on the EEC, there is very high risk to fish at the proposed maximum application rate of Cabrio EG. The MOS is 0.006.

Aquatic plants: The most sensitive endpoint for fresh water aquatic plants is the 120-h NOEC of diatoms based on biomass production (1.18 μg a.i./L). This is also the most sensitive aquatic endpoint. The MOS is 0.003 based on the EEC of 0.40 mg a.i./L. Therefore, there is a very high risk to aquatic plants at the proposed maximum application rate of Cabrio EG.

Non-target marine organisms: The most sensitive marine invertebrate endpoint is the 96-h NOEC for mysid shrimps (2.12 μg a.i./L). The most sensitive endpoint for marine fish is the 36 d- NOEC for fathead minnow (4.1 μg a.i./L). The most sensitive endpoint for marine algae is the 120-h NOEC for marine diatoms (9.7 μg a.i./L). Based on the EEC of pyraclostrobin in water, there is high to very high risk to marine invertebrates, fish and algae at the proposed maximum application rate of Cabrio EG. The MOS is 0.005 for mysids, 0.01 for fish, and 0.02 for diatoms.

6.5 Risk mitigation

Based on the data submitted, an assessment of the environmental safety associated with the use of Headline EC and Cabrio EG has identified the following concerns:

- application of Headline EC and Cabrio EG at the proposed label rate will pose a risk to fresh water invertebrates, fish, and algae
- application of Headline EC and Cabrio EG at the proposed label rate will pose a risk to marine invertebrates, fish and algae

The following are the mitigative measures:

- Observe the specified buffer zone.
- Include the following in the Environmental Precautionary Statement Section: "This product is toxic to aquatic invertebrates, fish and aquatic plants. Do not spray or contaminate aquatic areas (streams, lakes, ponds, rivers, tidal marshes and estuaries) through spray drift, cleaning of equipment or disposal of waste. Spray crops only from outside the planting away from the naturally vegetated area, shutting off the sprayer when turning at row ends. Terrestrial and aquatic buffer zone specifications provided should be observed".

Headline EC

INSTRUCTIONS FOR AERIAL APPLICATION:

Aerial drift is increased under certain meteorological conditions. Do not apply during periods of dead calm, when winds are gusty or when wind speed is greater than 16 km/hour at flying height at the site of application.

For the protection of non-target habitats, over-spray or drift to sensitive habitats must be avoided. A buffer zone of five metres is required between the downwind point of direct application and the closest edge of sensitive terrestrial habitats including grasslands, forested areas, shelter belts, woodlots, hedgerows, pastures, rangelands, and shrublands. The buffer zones specified in the table below are required between the downwind point of direct application and the closest edge of sensitive aquatic habitats such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs, and wetlands. Do not contaminate these habitats when cleaning and rinsing spray equipment or containers.

Aerial buffer zone—Headline

Crops	Aquatic buffer zone (m)
wheat, barley, rye, chick peas	90
field peas, lentils	50

INSTRUCTIONS FOR GROUNDBOOM APPLICATION:

Do not apply during periods of dead calm or when winds are gusty.

For the protection of non-target habitats, over-spray or drift to sensitive habitats must be avoided. The buffer zones specified in the table below are required between the downwind point of direct application and the closest edge of sensitive terrestrial habitats including grasslands, forested areas, shelter belts, woodlots, hedgerows, pastures, rangelands and shrublands. The buffer zones specified in the table below are required between the downwind point of direct application and the closest edge of sensitive aquatic habitats such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs, wetlands, and estuarine/marine habitats. Do not contaminate these habitats when cleaning and rinsing spray equipment or containers.

Buffer zone—Ground application—Headline

Crops	Aquatic buffer zone (m)	Terrestrial buffer zone (m)
field peas, lentils, dry beans	18	2
wheat, barley, rye, chick peas, grass grown for seeds	24	
sugarbeets, potatoes	35	5

Cabrio EG

INSTRUCTIONS FOR GROUNDBOOM APPLICATION

Do not apply during periods of dead calm or when winds are gusty.

For the protection of non-target habitats, over-spray or drift to sensitive habitats must be avoided. A buffer zone of two metres is required between the downwind point of direct application and the closest edge of sensitive terrestrial habitats including grasslands, forested areas, shelter belts, woodlots, hedgerows, pastures, rangelands, and shrublands. A buffer zone of 31 metres is required between the downwind point of direct application and the closest edge of sensitive aquatic habitats such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs, and wetlands. Do not contaminate these habitats when cleaning and rinsing spray equipment or containers.

INSTRUCTIONS FOR AIRBLAST APPLICATION:

Do not direct spray above trees/vines and turn off outward pointing nozzles at row ends and outer rows. Do not apply during periods of dead calm, when winds are gusty or when wind speed is greater than 16 km/h at the application site as measured outside of the orchard/vineyard on the upwind side.

For the protection of non-target habitats, over-spray or drift to sensitive habitats must be avoided. A buffer zone of two metres is required between the downwind point of direct application and the closest edge of sensitive terrestrial habitats including grasslands, forested areas, shelter belts, woodlots, hedgerows, pastures, rangelands, and shrublands. A buffer zone of 42 metres is required between the downwind point of direct application and the closest edge of sensitive aquatic habitats such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs, and wetlands. Do not contaminate these habitats when cleaning and rinsing spray equipment or containers.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended uses

BASF Canada Inc. (BAZ) has applied for the registration of two commercial class end-use products with the trade names Headline™ EC Fungicide and Cabrio EG™ EG Fungicide. These products contain respectively 250 g/L and 20% of the new active ingredient, pyraclostrobin technical fungicide. Both products are proposed for use on a large number of crops (see section 7.1.4.1).

7.1.2 Mode of action

Pyraclostrobin is a foliar fungicide belonging to the strobilurin chemical group. It is a synthetic analog of strobilurin A, a naturally occurring antifungal metabolite of the fungus *Strobillurus tenacellus*.

The active ingredient acts at the cellular level by inhibiting electron transport in the mitochondrial respiratory chain at the cytochrome-bc1 complex. The inhibition disrupts the energy producing systems of the fungal cell and can also result in the production of free radicals which leads to the breakdown of the mitochondrial and cytoplasmic membranes.

Pyraclostrobin acts protectively by inhibiting spore germination, germ tube growth and penetration into the host tissues. In certain host-pathogen relationships, curative effects have been observed like prevention of growth of established mycelium and sporulation, thereby controlling the spread of the disease. Pyraclostrobin exhibits strong translaminar mobility (movement from the upper leaf to the lower leaf surface). No root uptake or vapour phase activity has been observed.

7.1.3 Crops

(See section 7.1.4.1)

7.1.4 Effectiveness against pests

7.1.4.1 Headline EC

237 trials were reviewed to assess the efficacy of control claims on crop and pest combinations in terrestrial food crops and turf. See Appendix V for the table summarize the results of the efficacy review for Headline EC.

For ground sprays apply in at least 100 L of water/ha on cereals, pulses, grasses grown for seed and in a minimum of 50 L of water/ha for aerial. On potatoes and sugar beets apply by ground only in a minimum of 200 L of water/ha.

7.1.4.2 Cabrio EG

266 trials were reviewed to assess the efficacy of control claims on 39 crop and pest combinations in terrestrial food crops. Appendix V shows a table that summarizes the results of the value review for Cabrio EG. Only ground application was supported for this formulation.

7.1.5 Total spray volume

Headline EC should be applied in a minimum of 100 L of water/ha for ground spray and 50 L of water/ha for aerial. Cabrio EG is supported for ground application only in a minimum of 225 L of water/ha on blueberry, root vegetables, fruiting vegetables, and bulb vegetables, 350 L of water/ha in cucurbits and 1000 L of water/ha on stone crops and strawberries

7.2 Phytotoxicity to target plants (including different cultivars), or to target plant products

Cabrio EG demonstrated phytotoxicity on grape variety Niagara. Since azoxystrobin and krezoxim-methyl, two registered fungicides in the strobilurin group, have been shown to be extremely phytotoxic to certain apple and crabapple varieties and cherry varieties respectively; special attention was given to those crops. The data reviewed on apples and cherries did not show any phytotoxicity to those crops.

7.3 Observations on undesirable or unintended side effects e.g., on beneficial and other non-target organisms, on succeeding crops, other plants or parts of treated plants used for propagating purposes (e.g., seed, cutting, runners)

See section 7.2.

7.3.1 Impact on succeeding crops

Not required for fungicides.

7.3.2 Impact on adjacent crops

No phytotoxicity was noted in any of the trials submitted however azoxystrobin and krezoxim-methyl, two registered fungicides in the QoI group, have been shown to be extremely phytotoxic to certain apple and crabapple varieties and cherry varieties respectively. Given that the reviewed efficacy data on cherries showed no phytotoxic effects, phytotoxicity trials on apples and crabapples are required for Cabrio EG and Headline EC.

7.4 Economics

No information was provided on economic losses directly attributable to the proposed diseases.

7.5 Sustainability

7.5.1 Survey of alternatives

7.5.1.1 Non-chemical control practices

The use of non-chemical control practice always has an important role to play in the production of any crop. Any combination of the following practices can be used to prevent unnecessary fungicide applications.

- Use healthy seed.
- Use disease-resistant crop varieties and cultivars.
- Use of proper cultural practices (i.e., rotation with non-host crops, irrigation management to avoid prolonged periods of wetness).
- Follow an appropriate sanitation program to manage crop debris and eliminate sources of disease.

7.5.1.2 Chemical control practices

The number and type of available alternative fungicide products differ for the various pests proposed for Headline EC and Cabrio EG. The major fungicide active ingredients currently used for control of the proposed pests include, but are not necessarily limited to, those listed in Appendix V,Table 3. Each active listed is registered for the control of one or more disease.

7.5.2 Compatibility with current management practices including IPM

Not applicable.

7.5.3 Contribution to risk reduction

The two products fit well into IPM strategies due to their strong activity on multiple diseases and low risk to beneficial insects and other beneficial arthropods. They can also replace some of the older fungicides currently used through substitution of sprays or elimination of sprays due to the longer residual effect of pyraclostrobin.

7.5.4 Information on the occurrence or possible occurrence of the development of resistance

Pyraclostrobin belongs to the QoI group. Since the registration of the first QoI fungicide, disease resistance has been found in several crops and enhanced management strategies have been recommended by FRAC (Fungicide Resistance Action Committee). The North American QoI (NAQoI) Working Group, composed of the North American registrants of QoI fungicides (azoxystrobin, famoxadone, fenamidone, krezoxim methyl, pyraclostrobin, trifloxystrobin) has developed resistance management recommendations. Current population surveys have confirmed the presence of strobilurin resistant pathogens in the following crops: cereals, potatoes, grapes, cucurbits, pome fruits and bananas.

In order to maintain the sustainability and effectiveness of all strobilurins fungicides, it is essential to use specific resistance management options once resistance has been identified. Given that these recommendations are developed following isolation of resistant strains in commercial fields worldwide, they are incorporated in the use directions on the label in order to prevent the selection of resistant strains in Canada and the U.S. Furthermore, the following resistance management section for group 11 fungicide has been developed in consultation with the NAQoI Working Group and the U.S., EPA for inclusions on both Cabrio EG and Headline EC labels.

Resistance management
Cabrio EG/Headline EC contains pyraclostrobin, a group 11 fungicide, and is effective against pathogens resistant to fungicides with modes of action different from those of QoI fungicides (Target site group 11), for example dicarboximides, sterol inhibitors, benzimidazoles or phenylamides. Fungal isolates with acquired resistance to group 11

fungicides, such as pyraclostrobin, azoxystrobin, trifloxystrobin and kresoxim-methyl, may eventually dominate the fungal population if group 11 fungicides are used predominantly and repeatedly in the same field in successive years as the primary method of control for the targeted pathogen species. This may result in reduction of disease control by Cabrio EG/Headline EC or other group 11 fungicides. The following recommendations may be considered to delay the development of fungicide resistance:

1. **Applications:** Adhere to the label instructions regarding the consecutive use of Cabrio EG/Headline EC or other target site of action Group 11 fungicides that have a similar site of action on the same pathogens. To maintain the performance of Cabrio EG/Headline EC in the field, do not exceed the total number of sequential applications of Cabrio EG/Headline EC and the total number of applications of Cabrio EG/Headline EC per season as stated in the crop section of the label.

2. **IPM:** Cabrio EG/Headline EC should be integrated into an overall disease and pest management program. Cultural practices known to reduce disease development should be followed. Consult your local extension specialist, certified crop advisor and(or) BASF for additional IPM strategies established for your area. Cabrio EG/Headline EC may be used in Agricultural Extension advisory (disease forecasting) programs, which recommend application timing based on environmental factors favourable for disease development.

3. **Monitor:** Monitor efficacy of all fungicides used in the disease management program against the targeted pathogen and record other factors that may influence fungicide performance and(or) disease development.

4. **Reporting:** If a group 11 target site fungicide, such as Cabrio EG/Headline EC, appears to be less or no longer effective against a pathogen that it previously controlled or suppressed, contact a BASF-representative, local extension specialist, or certified crop advisor to assist in determining the cause of reduced performance.

7.6 Conclusions

The data available for review indicate that Headline EC can provide acceptable disease control or disease suppression on the following crop and disease combinations:

1. Chick peas for control of Ascochyta blight
2. Dry beans for control of anthracnose, Mycosphaerella blight, powdery mildew and rust.
3. Dry field peas for control of Mycosphaerella blight and powdery mildew
4. Lentils for control of Ascochyta blight and anthracnose
5. Potatoes for control of early blight and late blight.
6. Sugar beets for control of Cercospora leaf spot and powdery mildew

7. Barley for control of spot blotch, net blotch, scald and stripe rust
8. Rye for control of leaf rust and powdery mildew
9. Wheat for control of powdery mildew, leaf rust, Septoria leaf spot, spot blotch, stripe rust and tan spot.
10. Bluegrasses, fescues and ryegrasses grown for seeds for control of stem and leaf rust and suppression of powdery mildew.

The data available for review indicate that Cabrio EG can provide acceptable disease control or disease suppression on the following crop and disease combinations:

1. Blueberry (high bush and low bush) for control of anthracnose and Phomopsis.
2. Bulb vegetables (onions (all varieties), garlic, leek and shallot) for control of Alternaria purple blotch and downy mildew
3. Field cucumber, gherkin, muskmelon, pumpkin, citron melon, watermelon, winter squash, and summer squash for control of Alternaria blight, anthracnose, downy mildew, powdery mildew and gummy stem blight
4. Field peppers (bell, chili, cooking, sweet, pimento), eggplant and field tomato for control of early blight and anthracnose, and eggplant and field tomato for control of late blight.
5. Carrot, garden beet, turnip, rutabaga, oriental radish, radish and horseradish for the control of Alternaria, powdery mildew and Cercospora leaf spot.
6. Stone fruits (apricot, cherry (sweet and tart), nectarine, peach, plums and prune) for control of anthracnose and for suppression of Monilinia blossom and twig blight in all crops, and for control of powdery mildew in cherries (sweet and tart) only.
7. Strawberry for control of anthracnose.

Aerial application

Aerial application was requested for all crops. No aerial trial was submitted, however efficacy data using 150 g a.i./ha of Headline EC with a low water volume (25 to 50 L/ha) applied by ground to simulate aerial application in various crops was submitted in support of this claim. Although the low water dilution provided the same level of control as the regular ground application using 100 L/ha, bridging data using true aerial application is needed to confirm that aerial application does provide effective disease control. Also, in discussion with extension personnel it appeared that a 15 to 20% decrease in efficacy is "expected" when using aerial application due to insufficient canopy penetration. However, aerial application is sometime the only way to treat a crop due to various factors such as density and height of the canopy, size of the field, inability to enter the field with the application equipment following prolonged rains, time available to complete the application for effective disease control.

The surrogate data reviewed indicate that application at lower dilution volume can provide commercially acceptable disease control. However, aerial efficacy trials are still needed to confirm the validity of the surrogate data. Aerial application of Headline EC at the highest recommended rate for the specific disease/crop combination is acceptable for registration on chick pea, dry field beans, dry field peas, lentils, sugar beet, barley, rye and wheat. Aerial efficacy trials are requested on chick peas and potatoes to confirm the validity of the surrogate data. Aerial efficacy data on one stone fruit crop will be needed to support aerial application for Cabrio EG.

8.0 Toxic Substances Management Policy considerations

During the review of pyraclostrobin, PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this active ingredient and products do not meet TSMP Track-1 criteria because:

- Pyraclostrobin meets the criterion for persistence in soil. Its value for half-life in soil (277 d) is above the TSMP Track-1 cut-off criteria for soil (≥ 182 days). No acceptable studies were submitted to determine the persistence of pyraclostrobin in water. Pyraclostrobin is unlikely to volatilize, based on the vapour pressure and Henry's Law constant. Therefore, a study of persistence in air is not triggered. The half-life of pyraclostrobin in anaerobic soil was 3 d, which is below the TSMP cut-off criteria for sediment (≥ 365 days).

- Pyraclostrobin is not bioaccumulative. Studies have shown that the bioconcentration factor (BCF) is 232–1246, which is below the TSMP Track-1 cut-off criterion of BCF ≥ 5000.

- The toxicity of pyraclostrobin is described in Sections 3.1 and 6.0.

- Pyraclostrobin does not form any major transformation products that meet the TSMP Track-1 criteria.

- Pyraclostrobin (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track-1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

- The formulated products (Headline EC and Cabrio EG) do not contain any formulants, by-products or microcontaminants that are known to be TSMP Track-1 substances. All formulants in Cabrio EG are either EPA list 3 or list 4B.

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[1] The federal Toxic Substances Management Policy is available through Environment Canada's Web Site at : www.ec.gc.ca/toxics

[2] The PMRA's Strategy for Implementing the Toxic Substances Management Policy, DIR99-03, is available through the Pest Management Information Service: Phone 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); Fax (613) 736-3798; E-Mail pminfoserv@hc-sc.gc.ca or through our Web Site at www.hc-sc.gc.ca/pmra-arla

Headline EC contains a formulant, which is on the EPA List 2 Potentially Toxic Inerts.

9.0 Regulatory decision

The active ingredient pyraclostrobin and associated end-use products, Headline EC, for the control of tan spot, septoria leaf spot, leaf rust, powdery mildew, spot blotch, and stripe rust in wheat; net blotch, scald, spot blotch and stripe rust in barley; leaf rust and powdery mildew in rye; ascochyta blight in chick peas; anthranose and aschochyta in lentils; mycospaerella and powdery mildew in dry field peas; anthracnose, powdery mildew and rust in dry beans *Phaseolus* spp.; anthranose, mycosphaerella blight, powdery mildew and rust in dry beans *Vigna* spp.; mycoshaerella and powdery mildew in dry beans *Lupinus spp.*; and mycosphaerella and powdery mildew in faba beans; early blight and late blight in potatoes; Cercospora leaf spot and powdery mildew in sugar beets; stem and leaf rust and suppression of powdery mildew in bluegrasses, fescues and ryegrasses grown for seeds; and Cabrio, for the control of anthracnose and Phomopsis in highbush and lowbush blueberries; Alternaria purple blotch and downy mildew in Crop Group 3 bulb vegetables (onions (dry and green), garlic, leek and shallot); alternaria blight, anthranose, downy mildew, powdery mildew and gummy stem blight in field cucumber, gherkin, muskmelon, pumpkin, citron melon, watermelon, winter squash, and summer squash; early blight and anthracnose in field peppers (bell, chili, cooking, sweet, pimento), eggplant, and field tomato; late blight in eggplant and field tomato; Alternaria, powdery mildew and Cercospora leaf spot in carrot, garden beet, turnip, rutabaga, oriental radish, radish and horseradish; suppression of Monilinia blossom and twig blight and control of anthracnose in Crop Group 12 stone fruits (apricot, cherry (sweet and tart), nectarine, peach, plums, and prune); control of powdery mildew in cherries (sweet and tart), and anthracnose in strawberries have been granted temporary registration under Section 17 of the Pest Control Products Regulations subject to the generation of the following studies:

- A mouse oncogenicity study (DACO 4.4.3);
- A rat chronic/oncogencity (DACO 4.4.4) **OR** rat chronic (DACO 4.4.1) and rat oncogenicity (DACO 4.4.2);
- A rat reproduction study (DACO 4.5.1);
- Rat 28-day dermal toxicity study (DACO 4.3.4);
- In vivo dermal absorption study (Cabrio EG fungicide only);
- Radiovalidation and interlaboratory method validation of the poultry-specific LC/MS/MS method D9902;
- Freezer storage stability tests;
- Supervised residue trial studies;
- The biotransformation of pyraclostrobin in the aerobic water-sediment system;
- Non-target terrestrial plant toxicity of pyraclostrobin and acute toxicity of BF 500-3 to freshwater fish, freshwater invertebrates, and freshwater green algae
- Aerial efficacy trials.

List of abbreviations

a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
AFC	antibody-forming cell
AP	alkaline phosphatase
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
bw	body weight
bwg	body-weight gain
B cells	bursa derived lymphocytes
CAS	Chemical Abstracts Service
CD	cluster of differentiation (for naming cell surface molecules expressed on lymphocytes in immunology)
ConA	concavalin A
CSFII	Continuing Survey of Food Intakes by Individuals
d	day(s)
DBA	days between applications
DFR	dislodgeable foliar residue
DMS	dimethyl sulfate
DNA	deoxyribonucleic acid
EC	emulsifiable concentrate
EG	emulsifiable granules
EEC	expected environmental concentration
EPA	Environmental Protection Agency (U.S.)
FOB	functional observational battery
F0	parental animals
F1	1st generation offspring
F2	2nd generation offspring
GIT	gastro-intestinal tract
GSD	geometric standard deviation
IARC	International Agency for Research on Cancer
ILV	Independent Laboratory Validation
IUPAC	International Union of Pure and Applied Chemistry
K_{ow}	*n*-octanol/water partition coefficient
Kd	adsorption quotient
K_{oc}	adsorption quotient normalized to organic carbon
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
LPS	lipopolysaccharide
MIS	maximum irritation score
MAS	maximum average score (at 24, 48 and 72 hours)

MMAD	mass median aerodynamic diameter
MOE	margin of exposure
MRL	maximum residue level
MTD	maximum tolerated dose
MTDB	maximum theoretical dietary burden
NAFTA	North American Free Trade Agreement
NAQoI	North American Quinone outside Inhibitors (a North American FRAC group for the QoI = strobilurin fungicides)
NK	natural killer cell
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
OSHA	Occupational Safety and Health Administration
PFC assay	plaque-forming-cell assay
PC	positive control
pg	pico gram
PHED	Pesticide Handlers' Exposure Database
PMRA	Pest Management Regulatory Agency
PMA	phorbol myristate acetate
ppm	parts per million
ROC	residue of concern
SD	standard deviation
sRBC	sheep red blood cell preparation (T-cell dependent antigen)
T cells	thymic derived lymphocytes
T3	tri-iodothyronine
T4	thyroxine
TBC	thyroxine binding capacity
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TS	test substance
TSMP	toxic substances management policy
TWG	Technical Working Group
UDPGT	uridine 5'-diphosphatase-glucuronyl transferase
UDS	unscheduled deoxyribonucleic acid synthesis
µg	micrograms
µL	micro litre
UF	uncertainty factor
U.S.	United States of America
USDA	United States Department of Agriculture
UV	ultra-violet

Appendix I Residue Analysis

Table 1 Multi-residue methods for residue analysis

Protocols from existing multi-residue methods were found to be suitable for the determination of pyraclostrobin residues in grape and peanut nutmeat but unsuitable for the determination of the desmethoxy metabolite BF 500-3.

METHODS FOR RESIDUE ANALYSIS OF PLANTS AND PLANT PRODUCTS

ENFORCEMENT and DATA GATHERING METHOD
LC/MS/MS Method D9808 (U.S.) or 421/0 (Germany) (Limit of Quantitation: 0.02 ppm/analyte; Limit of Detection: 0.5 pg/µL)

RESIDUE OF CONCERN: Pyraclostrobin and the desmethoxy metabolite BF 500-3

Commodities	Spiking levels (ppm)	Range of recoveries (%)		Average recoveries (%)	
		Pyraclostrobin	BF 500-3	Pyraclostrobin	BF 500-3
Grape	0.02	87.5–92.4	86.6–89.1	89.5	88.1
	2	88.1–99.5	85.4–100.5	94.1	93.3
Average ± s.d. (cv) n=10				91.8 ± 4.4 (4.8)	90.7 ± 5.3 (5.9)
Orange	0.02	72.1–80.1	68.0–78.0	76.3	73.9
	2	82.6–92.1	76.9–87.6	86.8	82.6
Average ± s.d. (cv) n=10				81.6 ± 6.6 (8.1)	78.3 ± 6.3 (8.0)
Peanut nutmeat	0.02	74.8–82.1	71.7–79.0	78.5	76
	2	73.6–95.0	72.7–90.4	89	85.3
Average ± s.d. (cv) n=10				83.7 ± 8.4 (10.1)	80.6 ± 7.2 (8.9)
Wheat forage	0.02	90.9–98.9	88.9–97.9	94.9	92.1
	2	88.4–93.2	87.2–95.4	91.1	91.3
Average ± s.d. (cv) n=10				93.0 ± 3.1(3.3)	91.2 ± 3.3 (3.7)
Wheat grain	0.02	73.7–76.6	73.3–78.2	74.9	75.6
	2	84.4–93.6	83.3–91.3	90.1	86.8
Average ± s.d. (cv) n=9				83.4 ± 8.5 (10.2)	81.2 ± 6.5 (8.0)
Wheat straw	0.02	74.6–90.4	73.0–84.9	80.4	76.2
	2	75.9–85.7	66.8–76.8	82.4	73.4
Average ± s.d. (cv) n=10				81.4± 4.9 (6.0)	74.8 ± 4.5 (6.0)

ENFORCEMENT METHOD
HPLC/UV Method D9904 (Limit of Quantitation: 0.02 ppm/analyte; Limit of Detection: 2.0 ng/mL)

RESIDUE OF CONCERN: Pyraclostrobin and the desmethoxy metabolite BF 500-3

Commodities	Spiking levels (ppm)	Range of recoveries (%)		Average recoveries (%)	
		Pyraclostrobin	BF 500-3	Pyraclostrobin	BF 500-3
Grape	**0.02**	82–124	56–98	112	84
	2	85–110	77–103	98	90
Average ± s.d. (cv) n=10				105 ± 15 (14)	87 ± 13 (15)
Orange	**0.02**	89–115	96–120	99	104
	2	72–108	66–98	96	87
Average ± s.d. (cv) n=10				97 ± 12 (12)	96 ± 14 (15)
Peanut nutmeat	**0.02**	94–113	70–89	106	80
	2	98–105	84–90	102	88
Average ± s.d. (cv) n=10				104 ± 6 (6)	84 ± 7 (8)
Wheat forage	**0.02**	95–103	86–99	101	90
	2	91–99	83–91	95	87
Average ± s.d. (cv) n=10				98 ± 4 (4)	89 ± 5 (6)
Wheat grain	**0.02**	68–119	54–108	88	77
	2	97–104	84–92	101	89
Average ± s.d. (cv) n=9				94 ± 16 (17)	83 ± 16 (19)
Wheat straw	**0.02**	97–104	94–111	101	102
	2	77–89	69–80	85	76
Average ± s.d. (cv) n=10				93 ± 9 (10)	89 ± 15 (17)

CONFIRMATORY METHOD
LC/MS/MS acts as both a method to detect and quantitate the analytes of interest as a confirmatory method.

ENFORCEMENT METHOD
Enforcement methods are both the HPLC Method D9904 and LC/MS/MS D9808

INTERLABORATORY VALIDATION (ILV)
Interlaboratory validation indicated good reliability and reproducibility of both methods

Table 2 Methods for residue analysis of animal matrices

DATA GATHERING METHOD
HPLC/UV Method 439/0 (Limit of Quantitation: 0.05 ppm for tissues; 0.01 ppm in milk; Limit of Detection: 0.025 μg/mL)

RESIDUE OF CONCERN: Pyraclostrobin

Matrix	Spiking levels (ppm)	Range of recoveries (%)	Average recoveries (%) ± SD (CV)
Milk	0.01	67.9–89.2	76.9 ± 8.8 (11.5)
	0.1	78.5–92.2	86.9 ± 5.1 (5.9)
Average ± s.d. (cv) n=10			81.9 ± 8.6 (10.5)
Muscle	0.05	80.3–92.2	88.6 ± 5.4 (6.1)
	0.5	81.7–95.1	91.4 ± 5.5 (6.0)
Average ± s.d. (cv) n=10			90.0 ± 5.3 (5.9)
Liver	0.05	90.2–99.9	94.1 ± 3.9 (4.1)
	0.5	76.0–91.2	86.8 ± 6.3 (7.2)
Average ± s.d. (cv) n=10			90.5 ± 6.2 (6.9)
Kidney	0.05	77.9–89.8	83.9 ± 4.2 (5.1)
	0.5	83.3–92.7	89.6 ± 3.7 (4.2)
Average ± s.d. (cv) n=10			86.7± 4.8 (5.6)
Fat	0.05	82.6–88.8	85.7 ± 2.7 (3.2)
	0.5	82.4–98.9	93.9 ± 6.7 (7.1)
Average ± s.d. (cv) n=9			90.3 ± 6.6 (7.3)
Eggs	0.05	67.1–92.5	85.6 ± 10.5 (12.3)
	0.5	84.0–100.3	92.3 ± 6.9 (7.4)
Average ± s.d. (cv) n=10			89.0 ± 9.1 (10.2)

CONFIRMATORY METHOD
An HPLC/UV with modified parameters and conditions (autosampler, injection volume, column, flow rate and retention time) was proposed as a confirmatory method. No validation of the confirmatory method was provided.

ENFORCEMENT METHOD
Enforcement method is the same as the data gathering method.

INTERLABORATORY VALIDATION (ILV)
Interlaboratory validation indicated good reliability and reproducibility.

DATA GATHERING METHOD

LC/MS/MS Method 446/1 for ruminant matrices (Limit of Quantitation: 0.05 ppm/analyte for tissues; 0.01 ppm/analyte in milk; Limit of Detection: 2.5 ng/mL)

RESIDUE OF CONCERN: Pyraclostrobin and the metabolites hydrolyzable to BF 500-5 and BF 500-8

Matrix	**Spiking levels (ppm)**	**Range of recoveries (%)**		**Average recoveries (%) ± SD (CV)**	
		Pyraclostrobin	**BF 500-10**	**Pyraclostrobin**	**BF 500-10**
Milk	0.01	80.8–110.3	66.7–80.9	96.9 ± 11.2 (11.6)	73.5 ± 5.6 (7.6)
	0.1	61.1–71.3	58.4–63.6	66.5 ± 3.7 (5.6)	60.4 ± 2.1 (3.4)
Average ± s.d. (cv) n=5				81.7 ± 17.9 (21.9)	67.0 ± 8.0 (12.5)
Muscle	0.05	76.4–80.1	53.5–60.2	78.5 ± 1.7 (2.1)	56.1 ± 2.5 (4.4)
	0.5	80.0–86.1	53.9–55.5	83.1 ± 2.7 (3.2)	54.9 ± 0.7 (1.3)
Average ± s.d. (cv) n=5				80.8 ± 3.2 (4.0)	55.5 ± 1.8 (3.3)
Liver	0.05	73.8–87.5	62.3–68.1	80.0 ± 6.1 (7.6)	65.7 ± 2.7 (4.1)
	0.5	79.0–85.7	79.8–86.7	81.7 ± 2.6 (3.2)	82.4 ± 2.7 (3.2)
Average ± s.d. (cv) n=5				80.8 ± 4.5 (5.5)	74.0 ± 9.1 (12.4)
Kidney	0.05	80.2–92.9	62.2–70.5	85.6 ± 3.2 (7.3)	66.2 ± 3.1 (4.6)
	0.5	61.4–70.2	52.0–63.3	67.6 ± 3.6 (5.3)	60.2 ± 4.6 (7.7)
Average ± s.d. (cv) n=5				76.6 ± 10.6 (13.9)	63.2 ± 4.9 (7.7)
Fat	0.05	63.3–91.1	54.0–105.9	77.4 ± 11.6 (14.9)	83.4 ± 20.1 (24.1)
	0.5	80.2–101.3	68.2–101.7	90.6 ± 9.5 (10.5)	87.7 ± 12.9 (14.7
Average ± s.d. (cv) n=5				84.0 ± 12.2 (14.5)	85.6 ± 16.1 (18.8)

CONFIRMATORY METHOD

LC/MS/MS acts as both a method to detect and quantitate the analytes of interest as a confirmatory method. An additional confirmatory method was not necessary.

ENFORCEMENT METHOD

Enforcement method is the same as the data gathering method.

INTERLABORATORY VALIDATION (ILV)

Interlaboratory validation indicated that the liver sample had to be diluted to suppress the matrix interference effects. Once the dilution was incorporated, peak shapes were better defined and symmetrical. No difficulties were encountered with the other matrices. Overall the ILV was deemed acceptable in demonstrating good reliability and reproducibility.

DATA GATHERING METHOD
LC/MS/MS Method D9902 for poultry matrices (Limit of Quantitation: 0.05 ppm/analyte for tissues and eggs; Limit of Detection: 2.5 pg/μL)

RESIDUE OF CONCERN: Pyraclostrobin and the metabolites hydrolyzable to BF 500-5 and BF 500-9

Matrix	**Spiking levels (ppm)**	**Range of recoveries (%)**		**Average recoveries (%) ± SD (CV)**	
		Pyraclostrobin	**BF 500-16**	**Pyraclostrobin**	**BF 500-16**
Egg	0.05	102–131	53–67	115 ± 14 (12)	61 ± 7 (11)
	0.1	79–108	50–71	93 ± 13 (14)	63 ± 9 (14)
Average ± s.d. (cv) n=8				104 ± 17 (16)	62 ± 7 (11)
Liver	0.05	69–152	63–78	110 ± 35 (32)	68 ± 7 (10)
	0.1	85–110	71–76	99 ± 13 (13)	74 ± 2 (3)
Average ± s.d. (cv) n=8				104 ± 25 (24)	71 ± 6 (8)
Muscle	0.05	90–132	51–59	112 ± 18 (16)	55 ± 4 (7)
	0.1	101–115	56–62	108 ± 6 (6)	60 ± 3 (4)
Average ± s.d. (cv) n=8				110 ± 13 (12)	58 ± 4 (7)
Fat	0.05	91–100	60–91	95 ± 4 (4)	72 ± 13 (18)
	0.1	88–98	42–82	92 ± 4 (5)	65 ± 18 (28)
Average ± s.d. (cv) n=8				93 ± 4 (4)	68 ± 15 (22)

CONFIRMATORY METHOD
LC/MS/MS acts as both a method to detect and quantitate the analytes of interest as a confirmatory method. An additional confirmatory method was not necessary.

ENFORCEMENT METHOD
Enforcement method is the same as the data gathering method.

INTERLABORATORY VALIDATION (ILV)
No ILV submitted on the basis that this method is very similar to the LC/MS/MS Method 446/1 for ruminant commodities. Given the difficulties encountered with the ILV for Method 446/1, an ILV for this method should be submitted.

Table 3 Methods for environmental residue analysis

Matrix		BAS 500 F	BF 500-3	BF 500-4	BF 500-5	BF 500-6	BF 500-7
Soil	Method	LC/MS					
	Spike level	0.01–1.0 ppm					
	% Mean recovery (n)	93 ± 6 (24)	95 ± 8 (24)	93 ± 13 (24)	81 ± 13 (24)	96 ± 10 (24)	98 ± 8 (24)
	SD (%)	7	10	8	8	11	12
	LOQ	0.01 ppm					
Sediment	Method	LC/MS					
	Spike level	0.01–1.0 ppm					
	% Mean recovery (n)	92 ± 2 (15)	93 ± 4 (15)	*NP*	*NP*	98 ± 13 (15)	101 ± 15 (15)
	SD (%)	1.6	3.6	*NP*	*NP*	13	2.5
	LOQ	0.01 ppm					
Tap water	Method	LC/MS/MS					
	Spike level	0.05–5.0 ppb					
	% Mean recovery (n)	100 ± 5 (15)	*NP*	*NP*	*NP*	*NP*	*NP*
	SD (%)	4.6					
	LOQ	0.05 ppm					
Biota (fat)	Method	HPLC/UV at 270 nm					
	Spike level	0.05–0.5 ppm					
	% Mean recovery (n)	85.7 (5)	*NP*	*NP*	*NP*	*NP*	*NP*
	SD (%)	4.7					
	LOQ	0.05 ppm					

Matrix		**BAS 500 F**	**BF 500-3**	**BF 500-4**	**BF 500-5**	**BF 500-6**	**BF 500-7**
Biota (wheat and straw)	Method	LC/MS/MS					
	Spike level	0.02–2.0 ppm					
	% Mean recovery (n)	81.4 (10)	74.8 (10)	*NP*	*NP*	*NP*	*NP*
	SD	4.9	4.5				
	LOQ	0.02 ppm					

NP not provided

Matrix		**BF 500-11**	**BF 500-12**	**BF 500-13**	**BF 500-14**	**BF 500-15**
Soil		*NP*	*NP*	*NP*	*NP*	*NP*
Sediment		*NP*	*NP*	*NP*	*NP*	*NP*
Tap water	Method	LC/MS/MS				
	Spike level	0.05–5.0 ppb				
	% Mean recovery (n)	86 ± 8 (15)	102 ± 3 (15)	86 ± 6 (15)	103 ± 4 (15)	94 ± 5 (15)
	SD	8	2.9	6	3.9	4.6
	LOQ	0.05 ppb				
Biota		*NP*	*NP*	*NP*	*NP*	*NP*

NP not provided

Appendix II Toxicology Summaries

Table 1 Summary Table of Toxicology Studies for Pyraclostrobin

<table>
<tr><td colspan="4">METABOLISM—TECHNICAL</td></tr>
<tr><td colspan="4">In a series of rat metabolism studies, [^{14}C-tolyl]- or [^{14}C-chlorophenyl]-pyraclostrobin (≥98% radiochemical purity) was administered to Wistar rats (3-10/sex/dose) as a single gavage dose at 5 or 50 mg/kg bw or as a repeated gavage dose of 14 daily oral doses of pyraclostrobin at 50 mg/kg bw/d followed by a single oral dose of [^{14}C-tolyl]-pyraclostrobin at 5 mg/kg bw on day 15. In addition, another group of bile duct-cannulated rats (4 rats/sex) received a single gavage dose of [^{14}C-tolyl]-pyraclostrobin at 5 or 50 mg/kg bw.

Following oral dosing, [^{14}C]-pyraclostrobin was rapidly but incompletely absorbed (45–50%) from the G.I. tract of male and female rats. Biliary excretion accounted for 35–38% of the administered dose. Absorbed radioactivity was distributed in a similar manner for both sexes in all tissues and organs; the concentration in each was < 1 ppm at 120 hours post-dose. The excretion of radioactivity was rapid and primarily through the feces, accounting for 79% to 92% of the administered dose. Recovery from urine ranged from 11% to 16%. The excretion pattern was unchanged due to radiolabel, dose level or pre-treatment. There were many metabolites in excreta indicating extensive metabolic breakdown. The major metabolic pathways were N-demethylation and hydroxylation of the parent or glucuronide conjugates of a variety of phase I type metabolites. No sex-related differences were observed in the metabolic profile.</td></tr>
<tr><th>STUDY</th><th>SPECIES/STRAIN AND DOSES</th><th>NOAEL and LOAEL mg/kg bw/d</th><th>TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS</th></tr>
<tr><td colspan="4">ACUTE STUDIES—TECHNICAL</td></tr>
<tr><td>Oral</td><td>Rat—Wistar, 5/sex; 2000 and 5000 mg/kg bw</td><td>LD_{50}> 5000 mg/kg bw</td><td>Clinical observations consisted of dyspnea, apathy, staggering, piloerection and diarrhea—recovery by day 3. LOW TOXICITY</td></tr>
<tr><td>Dermal</td><td>Rat—Wistar, 5/sex; 2000 mg/kg bw</td><td>LD_{50}> 2000 mg/kg bw</td><td>Mild skin irritation was noted on the first day after dosing. LOW TOXICITY*</td></tr>
<tr><td>Inhalation</td><td>Rat—Wistar, 5/sex; 0, 0.31, 1.07 and 5.3 mg/L</td><td>0.31< LC_{50} < 1.07 mg/L</td><td>MMAD = 1–2.9 µm, GSD = 2.5–3.0
Clinical observations observed were irregular, accelerated and(or) intermittent breathing, bloody discharge from the nose, piloerection, smeared fur.
MODERATE TOXICITY
Label Recommendation:
WARNING POISON</td></tr>
<tr><td>Skin Irritation</td><td>Rabbit—NZW, 3/sex; 0.5 g dose</td><td>MAS = 2.2/8.0</td><td>Well-defined erythema began clearing at 72 hours, except for one case, which worsened. Irritation was still evident in two animals at study termination. Other findings were residual test substance, mechanical damage to the skin, scaling and irritation extending beyond the test site. Mildly irritating based on the MAS of 2.2/8.0; however, due to the persistence of irritation and spreading to beyond the treatment site, this was raised by a category and is therefore considered to be
MODERATELY IRRITATING
Label Recommendation:
WARNING SKIN IRRITANT</td></tr>
<tr><td>Eye Irritation</td><td>Rabbit—NZW, 1 male and 5 females; 0.1 mL dose (33 mg)</td><td>MAS = 4.6/110</td><td>MINIMALLY IRRITATING</td></tr>
</table>

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/d	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
Skin Sensitization (Maximization Test)	Guinea pig—Pirbright White Dunkin Hartley; 20 females in test group, 10 in control group. Test material administered 5% for induction; and 1% for challenge. Positive control reference data with alpha-hexylcinnamaldehyde 85%.	Test material elicited discrete to moderate erythema at 5% concentration. No evidence of sensitization. Positive control was sensitizing—demonstrating responsiveness of assay.	**NOT A SENSITIZER**
ACUTE STUDIES—FORMULATION (HEADLINE EC)			
NOTE: The solvent in this formulation is a petroleum distillate on U.S. EPA's List 2 of Inert Ingredients, and comprises 66.5% of the formulation. Any product containing ≥ 10% of a petroleum distillate is **required** to display the signal words **"CONTAINS PETROLEUM DISTILLATES"** on the primary panel of the label. **In addition, List 2 formulant ingredients may be subject to future regulatory action.**			
Oral	Rat—Wistar, 5/sex; 50, 200, 500 and 2000 mg/kg bw	LD_{50} : Males: 500 <LD_{50}<2000 mg/kg bw Females: 260 mg/kg bw Combined: 500 mg/kg bw	Clinical observations (observed on day of dosing only) consisted of poor general state, dyspnea, gasping, apathy, staggering, ataxia, paresis, twitching, saltatory spasm, rolling convulsions, extension/flexion spasm, opisthotonus, spasm of jaws, piloerection, diarrhea. Body weight gain was reduced in a dose-dependent manner. **HIGH TOXICITY** **Label Recommendation:** **DANGER POISON**
Dermal	Rat—Wistar, 5/sex; 4000 mg/kg bw	LD_{50}> 4000 mg/kg bw	Clinical signs (observed on day of dosing only) were dyspnea, apathy and poor condition. Very slight to severe erythema, and very slight to slight edema were observed with complete recovery by day 14. **LOW TOXICITY**
Inhalation	Rat—Wistar, 5/sex; 1.06, 2.72 and 5.2 mg/L	LC_{50} : Males: 3.76 mg/L Females: 3.27 mg/L Combined: 3.51 mg/L	MMAD = 0.9–1.3 μm, GSD = 3.4–3.8 Accelerated and intermittent breathing, bloody crust on nose, eyelid closure, high-stepping gait, squatting, piloerection, smeared fur—complete recovery by day 8. **LOW TOXICITY**
Skin Irritation	Rabbit—NZW, 2 males, 4 females; 0.5 mL dose	MAS = 4.33/8.0	Well-defined to moderate erythema was evident throughout the study; mild to well-defined edema at 24 and 48 hours. Erythema and edema extended beyond the area of exposure. Scaling observed for all animals on days 7 and 14. Moderately irritating based on the MAS of 4.33/8.0. However, based on severe scaling and persistence of irritation to day 14, this was raised by a category and was therefore considered to be **SEVERELY IRRITATING** **Label Recommendation:** **DANGER SKIN IRRITANT**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/d	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
Eye Irritation	Rabbit—NZW, 2 males, 4 females; 0.1 mL dose	MAS = 39.0/110	Mild corneal opacity to 72 hours; moderate effects on iris to 72 hours; conjunctival effects to day 7. In addition, suppuration, contracted pupil, bloody discharge, loss of corneal tissue to 72 hours. Moderately irritating based on the MAS of 39.0/110. **MODERATELY IRRITATING** **Label recommendation:** **WARNING EYE IRRITANT**
Skin Sensitization (Buehler method)	Guinea pig—Pirbright White Dunkin Hartley; 20 females in test group, 10 in control group. Test material administered 25% (0.5 mL) for induction; 5% (0.5 mL) for challenge. Positive control reference data with alpha-hexlycinnamaldehyde 85%.	Test material was minimally irritating at 25% concentration. No evidence of sensitization. Positive control was sensitizing—demonstrating responsiveness of assay.	**NOT A SENSITIZER**
ACUTE STUDIES—FORMULATION (CABRIO EG)			
Oral	Rat—Wistar, 5/sex; 500 and 2000 mg/kg bw	LD$_{50}$> 2000 mg/kg bw	One male and 1 female died on day 3 and hour 1, respectively. Clinical observations included dyspnea, apathy, piloerection and diarrhea. Females also exhibited staggering, salivation and shaking. Complete recovery by day 9. **LOW TOXICITY**
Dermal	Rat—Wistar, 5/sex; 2000 mg/kg bw	LD$_{50}$> 2000 mg/kg bw	Very slight or well-defined erythema observed on study day 1. **LOW TOXICITY**
Inhalation	Rat—Wistar, 5/sex; 1.00, 2.79 and 5.3 mg/L	LC$_{50}$: Males: 4.5 mg/L Females: 5.3 mg/L Combined: 4.7 mg/L	Clinical observations noted were accelerated respiration, respiratory sounds, crust on nose, eyelid closure, squatting and piloerection. Complete recovery by day 11. **LOW TOXICITY**
Skin Irritation	Rabbit—Himalayan, 6 males; 0.5 g dose	MAS = 1.2/8.0	Mild to well-defined erythema to 48 hours, mild erythema at 72 hours. **SLIGHTLY IRRITATING**
Eye Irritation	Rabbit—NZW, 4 males, 2 females; 0.1 mL dose	MAS = 9/110	Conjunctival redness and swelling with little discharge. No effects on cornea or iris. Complete recovery by day 3. **MINIMALLY IRRITATING**
Skin Sensitization (Buehler method)	Guinea pig—Pirbright White Dunkin Hartley; 20 females in test group, 10 in control group. Test material administered 60% (0.5 mL) for induction; 25% (0.5 mL) for challenge. Positive control reference data with alpha-hexlycinnamaldehyde 85%.	Test material was minimally irritating at 60% concentration. No evidence of sensitization. Positive control was sensitizing—demonstrating responsiveness of assay.	**NOT A SENSITIZER**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/d	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
SHORT TERM—TECHNICAL			
28-day dermal	Rats—Wistar, 10/sex/group; 0, 40, 100 and 250 mg/kg bw/d	**Systemic toxicity:** LOAEL could not be determined since there were no treatment-related systemic effects. NOAEL = 250 mg/kg bw/d. **Dermal toxicity:** LOAEL = 100 mg/kg bw/d. NOAEL = 40 mg/kg bw/d.	No systemic treatment-related effects at any dose level tested. **100 and 250 mg/kg bw/d:** Scale formation, hyperkeratosis, and epidermal thickening at the site of application. **MTD WAS NOT ATTAINED.**
28-day dietary	Rats—Wistar, 5/sex/group; 0, 20, 100, 500, or 1500 ppm (equal to 0, 1.8, 9.0, 42.3 and 120.2 mg/kg bw/d for males, and 0, 2.0, 9.6, 46.6 and 126.3 mg/kg/d for females)	LOAEL = 42.3/46.6 mg/kg bw/d NOAEL = 9.0/9.6 mg/kg bw/d.	**1.8/2.0 and 9.0/9.6 mg/kg bw/d:** No treatment-related findings. **42.3/46.6 mg/kg bw/d:** Increased spleen weight; increase in extramedullary hematopoiesis in the spleen; decreased RBC and Hgb (females); increased prothrombin time (males); decreased hepatocellular fat storage; duodenal mucosal hyperplasia. **120.2/126.3 mg/kg bw/d:** Decreased body weight gain and food intake (males); decreased RBC and Hgb (females); increased prothrombin time; decreased phosphorus and increased bilirubin (males); decreased glucose (females); increased spleen weight; increase in extramedullary hematopoiesis in the spleen; increased liver weight; decreased heptocellular fat storage; increased hepatocellular hypertrophy; duodenal mucosal hyperplasia.
90-day dietary	Mouse—B6C3F1; 10/sex/group; 0, 50, 150, 500, 1000 and 1500 ppm (equal to 0, 9.2, 30.4, 119.4, 274.4 and 475.5 mg/kg bw/d for males, and 0, 12.9, 40.4, 162.0, 374.1 and 634.8 mg/kg bw/d for females)	**Males**: LOAEL = 30.4 mg/kg bw/d NOAEL = 9.2 mg/kg bw/d **Females:** LOAEL = 12.9 mg/kg bw/d NOAEL could not be determined since there were treatment-related effects observed at all dose levels tested.	**12.9 mg/kg bw/d:** Ulcer/erosion of glandular stomach (females only). **30.4/40.4 mg/kg bw/d:** Increased urea; decreased triglycerides; ulcer/erosion of glandular stomach; increased apoptosis in lymph nodes, females only. **119.4/162.0 mg/kg bw/d:** Lower body weight gain; increased food intake; decreased WBC count (females only); decreased lymphocyte count, males only; increased urea; decreased triglycerides; decreased globulins, females only; thickening of mucosa of duodenum; thymus atrophy; ulcer/erosion of glandular stomach; increased apoptosis in lymph nodes. **274.4/374.1 mg/kg bw/d, and 475.5/634.8 mg/kg bw/d:** Decreased body weight gain; increased food intake; decreased WBC count; decreased monocyte and lymphocyte count (males only); decreased neutrophil count (females only); increased urea; decreased triglycerides; increased cholesterol; decreased total protein and globulins; thickening of the mucosa of the duodenum; thymus atrophy; ulcer/erosion of glandular stomach and increased apoptosis in the lymph nodes.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/d	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
90-day dietary	Rat—Wistar Chbb:THOM (SPF); 10/sex/group: 0, 50, 150, 500, 1000 and 1500 ppm (equal to 0, 3.5, 10.7, 34.7, 68.8 and 105.8 mg/kg bw/d for males, and 0, 4.2, 12.6, 40.8, 79.7 and 118.9 mg/kg bw/d for females).	LOAEL = 10.7/12.6 mg/kg bw/d NOAEL = 3.5/4.2 mg/kg bw/d	**10.7/12.6 mg/kg bw/d:** Extramedullary hematopoeisis (females only) and histiocytosis in the spleen. **34.7/40.8 mg/kg bw/d:** Increased spleen weight (females only); mucosal hyperplasia of the duodenum and hepatocyte hyperplasia, males only; extramedullary hematopoiesis (females only), sinus distension and histiocytosis in the spleen. **68.8/79.7 mg/kg bw/d:** Lower food intake; lower food efficiency (males only); decreased RBC count, Hgb and HCT (females only); increased total bilirubin; increased spleen weight; mucosal hyperplasia of the duodenum and hepatocyte hyperplasia, males only; extramedullary hematopoiesis (females only), sinus distension and histiocytosis in the spleen. **105.8/118.9 mg/kg bw/d:** Lower body weight gain; lower food intake; lower food efficiency; decreased RBC count, HCT and Hgb, higher reticulocyte count; increased total bilirubin; increased spleen weight; increased liver weight (females only); mucosal hyperplasia of the duodenum; hepatocyte hypertrophy; extramedullary hematopoiesis (females only), sinus distension and histiocytosis in the spleen.
90-day dietary	Dog—Beagle; 5/sex/group; 0, 100, 200 and 450 ppm (equal to 0, 2.8, 5.8 and 12.9 mg/kg bw/d for males, and 0, 3.0, 6.2 and 13.6 mg/kg bw/d for females)	LOAEL = 12.9/13.6 mg/kg bw/d NOAEL = 5.8/6.2 mg/kg bw/d	**12.9/13.6 mg/kg bw/d:** Transient vomiting; diarrhea; loss of body weight, decreased food intake and decreased food efficiency, females only; lower total protein, albumin and globulin; mucosal hypertrophy of the duodenum.
52-week dietary	Dog—Beagle; 5/sex/group; 0, 100, 200 and 400 ppm (equal to 0, 2.7, 5.4 and 10.8 mg/kg bw/d for males, and 0, 2.7, 5.4 and 11.2 mg/kg bw/d for females)	LOAEL = 10.8/11.2 mg/kg bw/d NOAEL = 5.4 mg/kg bw/d.	**10.8/11.2 mg/kg bw/d:** Transient vomiting; diarrhea; lower body weight gain, decreased food intake and decreased food efficiency, females only; lower cholesterol, total protein, albumin and globulin.
CHRONIC TOXICITY/ONCOGENICITY—TECHNICAL			
80-week dietary	Mouse—B6C3F1, 50/sex/group; 0, 10, 30, 120 ppm (both sexes) and 180 ppm (females only), (equal to 0, 1.4, 4.1 and 17.2 mg/kg bw/d for males, and 0, 1.6, 4.8, 20.5 and 32.9 mg/kg bw/d for females)	**Chronic Effects** LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 17.2/32.9 mg/kg bw/d. **Oncogenicity** No evidence of treatment-related oncogenicity.	**17.2/32.9 mg/kg bw/d:** Slightly lower body weight gain (non-adverse). No treatment-related oncogenic effects at any dose level tested. **MTD WAS NOT ATTAINED.**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/d	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
2-year dietary	Rat—Wistar, 20/sex/group; 0, 25, 75 and 200 ppm (equal to 0, 1.1, 3.4 and 9.0 mg/kg bw/d for males, and 0, 1.5, 4.6 and 12.3 mg/kg bw/d for females)	**Chronic Effects** LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 9.0/12.3 mg/kg bw/d. **Oncogenicity** No evidence of treatment-related oncogenicity.	**9.0/12.3 mg/kg bw/d:** Slightly lower body weight gain (non-adverse). No treatment-related oncogenic effects at any dose level tested. **MTD WAS NOT ATTAINED.**
2-year dietary	Rat—Wistar, 50/sex/group; 0, 25, 75 and 200 ppm (equal to 0, 1.2, 3.4 and 9.2 mg/kg bw/d for males, and 0, 1.5, 4.7 and 12.6 mg/kg bw/d for females)	**Chronic Effects** Males: LOAEL = 9.2 mg/kg bw/d Females: LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 12.6 mg/kg bw/d. **Oncogenicity** No evidence of treatment-related oncogenicity.	**9.2/12.6 mg/kg bw/d:** Slightly lower body weight gain (non-adverse). Acanthosis and ulcers in the forestomach, and an increased incidence of erosions/ulcers in the glandular stomach, males only. However, all but the incidence of ulceration of the glandular stomach fell within the historical control range of values. The toxicological significance of these findings is uncertain. No treatment-related oncogenic effects at any dose level tested. **MTD WAS NOT ATTAINED.**
REPRODUCTION/DEVELOPMENTAL TOXICITY—TECHNICAL			
Two-generation dietary, one litter per generation	Rat—Wistar, 25/sex/group; 0, 25, 75 and 300 ppm (equal to 0, 2.5, 7.4 and 29.0 mg/kg bw/d for males, and 0, 2.6, 7.8 and 30.4 mg/kg bw/d for females)	**Systemic Toxicity** LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 300 ppm (29.0 mg/kg bw/d for males and 30.4 mg/kg bw/d for females). **Reproductive Toxicity** LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 300 ppm (29.0 mg/kg bw/d for males and 30.4 mg/kg bw/d for females). **Offspring Toxicity** LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 300 ppm (29.0 mg/kg bw/d for males and 30.4 mg/kg bw/d for females).	**29.0/30.4 mg/kg bw/d:** Slightly lower body weight gain (non-adverse). No treatment-related reproductive effects at any dose level tested. **29.0/30.4 mg/kg bw/d:** F_1 and F_2 pup body weights slightly lower on days 14 and 21, and days 7, 14 and 21, respectively (non-adverse). Time to vaginal opening increased by 5% (non-adverse). **MTD WAS NOT ATTAINED.**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/d	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
Teratogenicity oral gavage	Rat—Wistar, 25/group; 0, 10, 25 and 50 mg/kg bw/d	**Maternal Toxicity** LOAEL = 25 mg/kg bw/d NOAEL = 10 mg/kg bw/d	**25 and 50 mg/kg bw/d:** Lower body weight gain and food consumption.
		Developmental Toxicity LOAEL could not be determined since there were no treatment-related findings. NOAEL = 50 mg/kg bw/d	No treatment-related developmental or teratogenic effects noted at any dose level tested.
Teratogenicity oral gavage	Rabbit—Himalayan, 25/group; 0, 5, 10 and 20 mg/kg bw/d	**Maternal Toxicity** LOAEL = 10 mg/kg bw/d NOAEL = 5 mg/kg bw/d	**10 and 20 mg/kg bw/d:** Reduced fecal output and blood in the bedding, increased weight loss at initiation of dosing, decreased food consumption (20 mg/kg bw/d), lower gravid uterus weight.
		Developmental Toxicity LOAEL = 10 mg/kg bw/d NOAEL = 5 mg/kg bw/d	**20 mg/kg bw/d:** Increased resorptions, increased total litter loss, increased post-implantation loss, decreased litter size. **10 mg/kg bw/d:** Increased resorptions, increased total litter loss.
		Teratogenicity Treatment-related teratogenic effects observed at 20 mg/kg bw/d.	An increased incidence of fetal/litter malformations was noted in the 20 mg/kg bw/d group due to an increased incidence of absent/misshapen lumbar vertebrae.
Teratogenicity oral gavage **SUPPLEMENTARY**	Rabbit—Himalayan, 25/group; 0, 1, 3 and 5 mg/kg bw/d	**Maternal Toxicity** LOAEL could not be determined since there were no adverse treatment-related findings at any dose level tested. NOAEL = 5 mg/kg bw/d	**1, 3 and 5 mg/kg bw/d:** Slightly lower body weight gain and food intake, considered to reflect normal biological variation, and not considered adverse.
		Developmental Toxicity LOAEL and NOAEL could not be determined since fetal assessment for developmental variations and malformations was not conducted.	**1, 3 and 5 mg/kg bw/d:** No treatment-related developmental effects (i.e., mean number of corpora lutea, total implantations, resorptions and live fetuses, pre- and post-implantation losses, placental weights and fetal body weights).
		Teratogenicity No evidence of treatment-related teratogenicity.	There were no treatment-related teratogenic effects noted at any dose level tested.
STUDY	**SPECIES/STRAIN or CELL TYPE**	**DOSES EMPLOYED**	**SIGNIFICANT EFFECTS/COMMENTS**
MUTAGENICITY—TECHNICAL			
S. typhimurium/E. coli Ames test	*S. typhimurium*— TA 98, TA 100, TA 1535 and TA 1537 *E. coli*—WP2 uvrA	0, 20, 100, 500, 2500 and 5000 µg/plate, ± S9	Negative
Gene mutation assay	Chinese Hamster Ovary (CHO) cells	Experiment 1: 0.625, 1.25, 2.5, 5.0, 10.0 and 20.0 µg/mL, ± S9 Experiment 2: 3, 4, 5, 6, 7 and 8 µg/mL, -S9 Experiment 3: 1.25, 2.5, 5.0, 10.0 and 20.0 µg/mL, ±S9	Negative

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS
Mammalian chromosome aberration assay	V79 cell cultures	Experiment 1: 0.0, 6.25, 12.5 and 25.0 µg/mL, ±S9 Experiment 2: 0.0, 3.125, 6.25 and 12.5 µg/mL, +S9 0.0, 0.005, 0.010, 0.050 and 0.100 µg/mL, -S9	Negative
Micronucleus assay	NMRI mice	0, 75, 150 and 300 mg/kg bw	Negative
Unscheduled DNA synthesis	Primary rat hepatocyte cultures	Experiment 1: 0.01, 0.03, 0.1, 0.3 and 1.0 µg/mL Experiment 2: 0.004, 0.02 and 0.5 µg/mL	Negative
NEUROTOXICITY—TECHNICAL			
Acute oral gavage	Rat—Wistar, 10/sex/group; 0, 100, 300 and 1000 mg/kg bw.	**Systemic Toxicity** **Males:** LOAEL = 1000 mg/kg bw NOAEL = 300 mg/kg bw **Females:** LOAEL could not be determined since there were no adverse, treatment-related effects at any dose level tested. **Neurotoxicity** LOAEL could not be determined since there were no treatment-related neurotoxic effects. NOAEL = 1000 mg/kg bw.	**1000 mg/kg bw:** Lower body weight gain, males only. No treatment-related neurotoxic effects were noted at any dose level tested.
13 week feeding study	Rat—Wistar, 10/sex/group; 0, 50, 250 and 750(m)/1500(f) ppm (equal to 0, 3.5, 16.9 and 49.9 mg/kg bw/d for males and 0, 4.0, 20.4 and 111.9 mg/kg bw/d for females)	**Systemic toxicity** LOAEL = 49.9/111.9 mg/kg bw/d NOAEL = 16.9/20.4 mg/kg bw/d **Neurotoxicity** LOAEL could not be determined since there were no treatment-related neurotoxic effects. NOAEL = 49.9/111.9 mg/kg bw/d.	**49.9/111.9 mg/kg bw/d:** Lower body weight gain, food intake and food efficiency. No treatment-related neurotoxic effects were noted at any dose level tested.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS

Recommendation for ARfD: For females 13+ years: 0.017 mg/kg bw/d, based on the lowest NOAEL of 5 mg/kg bw/d in the rabbit teratology study, and using a 300-fold uncertainty factor. This is based on the standard uncertainty factor of 100 with an additional 3-fold uncertainty factor due to the severity of the toxicological endpoint, i.e., increased resorptions/litter and increased total resorptions.

Recommendation for ADI/risk assessment: An MTD was not attained in the mouse oncogenicity study, rat oncogenicity study, rat chronic study, rat reproduction study and 28-day dermal study. In the absence of these data at appropriate doses, a definitive ADI could not be determined. However, based on the absence of adverse effects in these studies at all dose levels tested, it is considered appropriate to conduct an interim risk assessment based on a margin of exposure (MOE) approach. The most appropriate toxicological endpoint is duodenal hyperplasia, which may progress to neoplasia following long-term exposure. The lowest NOAEL for duodenal hyperplasia was 9.0/9.6 mg/kg bw/d, which was seen in the 28-day rat dietary study. However, all genotoxicity studies yielded negative results, indicating that pyraclostrobin is non mutagenic. The PMRA therefore considered that for an interim period of 5 years (i.e., until repeated cancer data is generated), an MOE of 3000× (i.e., 10× for interspecies differences, 10× for intraspecies differences, 10× for data deficiencies and 3× for the increase in the qualitative susceptibility of the rabbit fetuses) would provide an adequate margin of safety for this endpoint.

There was no indication of increased susceptibility of pups in the rat reproductive toxicity study.

There was an increase in the qualitative susceptibility of the prenatal development of rabbit fetuses following in utero exposure to pyraclostrobin.

Pyraclostrobin was teratogenic to rabbit fetuses at 20 mg/kg bw/d (maternally toxic dose).

There was no evidence of oncogenic potential of pyraclostrobin up to the highest dose levels tested in the long-term studies of 17.2/32.8 mg/kg bw/d in mice, and 9.2/12.6 mg/kg bw/d in rats. However, MTDs were not achieved in these studies. All mutagenicity assays yielded negative results.

There was no evidence of neutotoxicity in rats after acute and short-term exposure to pyraclostrobin.

Table 2 Mixer/loader/applicator exposure for Headline EC

Occupational scenario	Exposure[1] (mg/kg bw/d)	Margin of exposure (based on a NOAEL of 5 mg/kg bw/d[2])
Wheat—mixer/loader + groundboom application (farmer)[3]	0.0136	368
Wheat—mixer/loader + groundboom application (custom)[3]	0.0101	494
Wheat—mixer/loader (for aerial application)[3]	0.0082	608
Wheat—aerial application[3]	0.0045	1109
Lentil—mixer/loader + groundboom application (farmer)[4]	0.0009	548
Lentil—mixer/loader + groundboom application (custom)[4]	0.0072	695
Lentil—mixer/loader (for aerial application)[4]	0.0055	912
Lentil—aerial application [4]	0.003	1661
Potato—mixer/loader + groundboom application (farmer)	0.0009	536
Potato—mixer/loader + groundboom application (custom)	0.0196	256 [5]
Sugar Beet—mixer/loader + groundboom application (farmer)	0.0065	774
Grass Grown for Seed—mixer/loader + groundboom application (farmer)	0.0134	374
Grass Grown for Seed—mixer/loader + groundboom application (custom)	0.0109	457

[1] Based on a closed mixing and loading system for custom applicators and open mixing and loading for farmers with mixer/loaders wearing a single layer and gloves, groundboom and aerial applicators wearing a single layer and no gloves. For custom groundboom application, a closed cab scenario was used; for all other groundboom application scenarios (i.e., farmer), an open cab scenario was used.

[2] Based on the rabbit developmental study

[3] Wheat is the representative crop for wheat, barley, rye and chick peas

[4] Lentils are the representative crop for lentils, field peas (dry) and field beans (dry)

[5] Considered conservative as inputs to the exposure assessment (e.g., acreage treated per day) were conservative

Table 3 Mixer/loader/applicator exposure to Cabrio EG

Occupational scenario	Exposure[1] (mg/kg bw/d)	Margin of exposure (based on a NOAEL of 5 mg/kg bw/d[2])
Bulb Vegetables (onion)[3]—mixer/loader + groundboom application	0.0049	1020
Cucurbit Vegetables (field cucumber)[4]—mixer/loader + groundboom application	0.002	2538
Cucurbit Vegetables (cantaloupe, squash)[4]—mixer/loader + groundboom application	0.0037	1359
Fruiting Vegetables (field peppers)[5]—mixer/loader + groundboom application	0.0035	1425
Fruiting Vegetables (field tomatoes)[5]—mixer/loader + groundboom application	0.0023	2137
Root Vegetables (carrot)[6]—mixer/loader + groundboom application	0.0066	763
Highbush blueberries—mixer/loader + airblast application	0.0065	775
Lowbush blueberries—mixer/loader + groundboom application	0.0018	2857
Strawberries—mixer/loader + groundboom application	0.0006	8621
Stone Fruits (peach)[7]—mixer/loader + airblast application	0.0108	463
Stone Fruits (cherries)[7]—mixer/loader + airblast application	0.0022	2326

[1] Based on individuals wearing a single layer of clothing and gloves except for the groundboom applicators in which exposure was estimated for applicators not wearing gloves (insufficient gloves replicates)

[2] Based on a rabbit developmental study

[3] Onion is the representative crop for bulb vegetables

[4] Field cucumber, cantaloupe and squash are the representative crops for cucurbit vegetables

[5] Field peppers and field tomatoes are the representative crops for fruiting vegetables

[6] Carrots are the representative crop for root vegetables

[7] Peaches and cherries are the representative crops for stone fruits

Table 4 Re-entry intervals for Headline EC fungicide

Crop(s)	Transfer co-efficient ($\mu g/cm^2$)[1]	Re-entry interval (days)	Activities
Wheat, Barley, Rye, Chick peas and Lentils	1500	2	- Scouting and irrigation
Field Beans and Peas (dry)	2500	3	- Hand harvesting
	1500	2	- Scouting and irrigation
Sugar Beets	1500	2	- Scouting and irrigation
Potatoes	1500	2	- Scouting

[1] Agricultural Reentry Task Force (ARTF) Proprietary Transfer Coefficient. The applicant BASF is a member of ARTF.

Table 5 Re-entry intervals for Cabrio EG fungicide

Crop	Transfer co-efficient ($\mu g/cm^2$)[1]	Re-entry interval (days)	Activities
Green Onions (Bulb Vegetables)[2]	2500	3	- Hand harvesting and thinning
	300	0	- All other activities
Field Cucumbers (Cucurbit Vegetables)[3]	2500	3	- Hand harvesting, thinning and hand pruning
	1500	1	- All other activities
Field Tomatoes (Fruiting Vegetables)[4]	1000	0	- All activities
Carrots (Root Vegetables)[5]	2500	3	- Hand harvesting
	300	0	- All other activities
Highbush Blueberries	5000	29	- Hand harvesting
	1000	0	- All other activities
Lowbush Blueberries	1500	1	- Hand harvesting and pruning
	400	0	- All other activities
Strawberries	1500	1	- Hand harvesting, pinching, hand pruning and training

Crop	Transfer co-efficient ($\mu g/cm^2$)[1]	Re-entry interval (days)	Activities
Peaches (Stone Fruits)[6]	3000	10	- Hand harvesting and thinning
	1000	0	- All other activities

[1] ARTF Proprietary Transfer Coefficient. The applicant BASF is a member of ARTF.

[2] Green onions are the representative crop for bulb vegetables

[3] Field cucumbers are the representative crop for cucurbit vegetables

[4] Field tomatoes are the representative crop for fruiting vegetables

[5] Carrots are the representative crop for root vegetables

[6] Peaches are the representative crop for stone fruits

Table 6 Proposed MRLs

RAC and(or) processed commodity	MRL (ppm)
Dried shelled pea and bean (except soybean) (Crop Subgroup 6C: bean (adzuki, broad dry, dry, kidney, lablab, lima dry, moth, mung, navy, pink, pinto, rice, tepary, urd), catjang, chick pea, cowpea, guar, lentil, lupin (grain, sweet) and pea (blackeyed, crowder, field, pigeon and southern))	0.5
Tuberous and corm vegetables (Crop Subgroup 1C: arracacha, arrowroot, artichoke (chinese, Jerusalem), canna (edible), cassava, chayote root, chufa, dasheen, ginger, leren, potato, sweet potato, tanier, turmeric and yam (bean, true))	0.04
Sugar beets	0.15
Barley	0.4
Wheat	0.2
Rye	0.04
Root vegetables (Crop Subgroup 1B: beet (garden), burdock (edible), carrot, celeriac, chervil (turnip rooted), chicory, ginseng, horseradish, parsley (turnip rooted), parsnip, radish (oriental), rutabaga, salsify (black, spanish), skirret and turnip)	0.4
Bulb vegetables (Crop Group 3: garlic (great headed), leek, onion (dry bulb, green, potato, tree, Welsh) and shallot)	0.65
Fruiting vegetables (Crop Group 8: chili, eggplant, groundcherry, pepino, field pepper (bell, nonbell, nonbell sweet), tomatillo and field tomato)	1.0
Cucurbit vegetables (Crop Group 9: balsam apple, balsam pear, cantaloupe, chayote, field cucumber (chinese), gherkin (West Indian), gourd (edible), melon (citron), muskmelon, pumpkin, squash (summer, winter), watermelon and waxgourd (chinese))	0.5
Stone fruits (Crop Group 12: apricot, cherry (sweet, tart), nectarine, peach and plum (chickasaw, damson, Japanese, prune, fresh prune))	
Berries (Crop Group 13: blackberry, blueberry, caneberry, currant, elderberry, gooseberry, huckleberry, loganberry and raspberry)	0.7
Strawberry	1.0
Grapes	
Raisins	0.4
Fat and meat of cattle, goats, hogs, horses and sheep	2.0
Meat by-products except liver of cattle, goats, hogs, horses and sheep	7.0
Liver of cattle, goats, hogs, horses and sheep	0.1
Milk	0.2
	1.5
	0.1

Table 7 Proposed import tolerances

RAC and(or) processed commodity	**Tolerance (ppm)**
Banana	0.04
Citrus Fruits (Crop Group 10: calamondin, citron, citrus hybrids, grapefruit, kumquat, lemon, lime, mandarin (satsuma), orange (sour, sweet), pummelo, tangelo and tangerine)	0.7
Citrus, oil	4.0
Tree Nuts (Crop Group 14 which includes almond, beechnut, butternut, cashew, chestnut, chinquapin, filbert, nut (brazil, hickory, macadamia), pecan and walnut)	0.04
Peanut	0.05
Peanut, refined oil	0.1
Pistachio	0.5

Appendix III Integrated food residue chemistry summary

NATURE OF THE RESIDUE—ANIMALS	Lactating goats and Leghorn laying hens
Radiolabelling positions	[Chlorophenyl-U-^{14}C] pyraclostrobin and [Tolyl-U-^{14}C] pyraclostrobin
Proposed metabolic pathway	After five consecutive days of dosing (lactating goats; 12 ppm—low dose and 70 or 78 ppm—high dose, poultry; 12 ppm), 61–93% of the administered dose was excreta-related. There was minimal transfer of ^{14}C-residues in milk, eggs, tissues and organs (<1.0% of administered dose). In the lactating goat, pyraclostrobin was the predominant residue in muscle, fat and liver (tolyl label only). Pyraclostrobin was also identified in milk and kidney, however the parent compound was not resolved from the desmethoxy metabolite (BF 500-3). In the chlorophenyl label liver sample, the predominant metabolite was identified as BF 500-5 (resulting from the acid hydrolysate). In the laying hen, pyraclostrobin and the desmethoxy metabolite were found at equivalent concentrations in eggs. The desmethoxy metabolite BF 500-3 was the predominant residue in fat while its glucose conjugate (500M32) was the major residue in liver. Several additional metabolites were identified in fat, eggs, milk, tissues and excreta, however none appeared to be of toxicological concern and present at concentrations greater than 0.1 ppm. The metabolic pathway of pyraclostrobin in ruminants and poultry appeared to proceed predominantly via hydrolysis of the N-methoxy group of the parent compound yielding the desmethoxy metabolite, BF 500-3, hydroxylation of the chlorophenyl, pyrazole and(or) tolyl rings followed by conjugation. The metabolism of pyraclostrobin also involved the cleavage of the ether linkage.
Residue of concern (ROC)	For enforcement and risk assessment purposes, the ROC was defined as pyraclostrobin and the metabolites convertible to BF 500-5 for ruminant matrices and BF 500-9 for poultry matrices.
Comparison of metabolic profiles	The metabolic profile of pyraclostrobin was similar in goat, hen and rat, however the metabolism pattern in rat appeared to involve additional glucuronide conjugation not seen in the goat and hen. Despite these minor differences, the overall comparison of the identified metabolites demonstrated that the metabolism of pyraclostrobin in all three species proceeded via the same major metabolic pathways, therefore, a swine metabolism study was not required.

NATURE OF THE RESIDUE—PLANTS	Potato, grape and wheat
Radiolabelling positions	[Chlorophenyl-U-^{14}C] pyraclostrobin and [Tolyl-U-^{14}C] pyraclostrobin
Proposed metabolic pathway	Based on the data from the three metabolism studies, pyraclostrobin was the predominant residue in grapes, potato foliage, wheat forage and straw and chlorophenyl-labelled mature potato tubers and wheat grain. In tolyl-labelled potato tubers and wheat grain, the major identified residue was the amino acid L-tryptophan. The desmethoxy metabolite (BF 500-3) was also a significant component in grapes, potato tubers and foliage and wheat grain, forage and straw. Additional minor metabolites were identified in the RACs, however, none appeared to be of toxicological concern and present at concentrations greater than 0.1 ppm. The metabolic pathway of pyraclostrobin in plants seemed to proceed predominantly via the demethoxylation in the side chain of the tolyl moiety producing the desmethoxy metabolite (BF 500-3) followed by methoxylation of the phenyl ring. Also observed was the cleavage between the chlorophenyl and the tolyl moieties. In the potato and wheat metabolism studies, the amino acid L-tryptophan was formed from an anthranilic acid intermediate, via the shikimate pathway. Metabolite conjugation also represented a predominant pathway in the metabolism of pyraclostrobin in plants. The wheat translocation study demonstrated that very little radioactivity translocated from the treated leaves to the untreated plant parts.
Residue of concern (ROC)	For enforcement and risk assessment purposes, the ROC was defined as pyraclostrobin and the desmethoxy metabolite BF 500-3.
Novel plant metabolites	The metabolite 500M76, a structural isomer of pyraclostrobin, was only detected in wheat forage and straw. Apparently, this isomer was formed by intramolecular arrangement under the influence of light. This was corroborated by the photolysis study which demonstrated that this metabolite was the predominant residue. Since this metabolite was present at very low concentrations in forage and straw, it is not expected to transfer and subsequently bioconcentrate in tissues and milk. Therefore, additional animal metabolism studies involving dosing with this novel plant metabolite will not be required.

RESIDUE ANALYTICAL METHOD	PLANT MATRICES	
	LC/MS/MS method D9808 (U.S.) or 421/0 (Germany)	HPLC/UV Method D9904
Method ID	Validation of BASF Analytical Method No. 421/0 (Germany) D9808 (U.S.): Determination of BAS 500 F and its Metabolite BF 500-3 in Wheat, Grape, Peanut and Orange Matrices	Validation of BASF Analytical Method D9904, Method for Determination of BAS 500 F and Its Metabolite BF 500-3 Residues in Plant Matrices Using HPLC/UV
Analytes	Pyraclostrobin (BAS 500 F) and the desmethoxy metabolite (BF 500-3)	Pyraclostrobin (BAS 500 F) and the desmethoxy metabolite (BF 500-3)
Instrument	PE Sciex API 300 Biomolecular Mass Analyzer Inlet [HPLC System]: Shimadzu LC 10AD Binary Gradient Pump and Perkin Elmer 200 Series Auto Sampler	HP 1100 HPLC with variable wavelength detector and column switching capability
Instrument Parameters	Injection volume: 10 µL (or higher) Mobile phase [Isocratic]: MeOH: 4mM ammonium acetate in water: formic acid 80:19.9:0.1 Flow rate: 200 µL/min. Ionization mode: Positive Transitions: BAS 500 F 388 → 194 BF 500-3 358 → 164	Injection volume: 250 µL Column oven temperature: 25°C Mobile phase Column 1 [Gradiant]: Solvent A: ACN:MeOH:H_2O 20:10:70 Solvent B: ACN:MeOH:H_2O 45:10:45 Solvent C: ACN:H_2O 95:5 Column 2 [Isocratic]: ACN:MeOH:H_2O 45:10:45 Column switching: 16.9–18.4 minutes Flow rates: 400 µL/min for Column 1 500 µL/min for Column 2 Length of run: 35 minutes Detector wavelength: 276 nm
Column	Inertsil Phenyl 5 µm, 50 mm × 2.0 mm	Column 1: Luna Phenyl hexyl 100 mm 2.1 mm, 3 µm particle size. Column 2: Betasil 5 C18, 100 mm × 2.0 mm, 5µm particle size.
Standardization method	An external standard method was used as marker for retention time, response and calibration	An external standard method was used as marker for retention time, response and calibration
Stability of primary and(or) secondary standard solutions	No decomposition occurred for 120 days when standard solutions were made in methanol, kept in amber bottles with Teflon-lined screw caps and stored in the refrigerator.	No decomposition occurred for 120 days when standard solutions were made in acetonitrile, kept in amber bottles with Teflon-lined screw caps and stored in the refrigerator.
Retention times of ROC	BAS 500 F = ~ 2.0 minutes BF 500-3 = ~ 1.5 minutes	BAS 500 F = ~ 27 minutes BF 500-3 = ~ 26 minutes

Limit of detection (LOD)	0.5 pg/μL	2.0 ng/mL
Limit of quantitation (LOQ)	0.02 ppm/analyte	0.02 ppm/analyte
Repeatability	The relative standard deviations measured with respect to recoveries following spiking of BAS 500F and BF 500-3 at the limit of quantitation (0.02 ppm/analyte) were less than 10% for all plant matrices. The values obtained are indicative of the method having good repeatability.	The mean relative standard deviations at spiking levels of 0.02–2.0 mg/kg for BAS 500 F and BF 500-3 in various plant matrices ranged from 4 to 17% and 6 to19%, respectively. In most cases, the relative standard deviations measured with respect to recoveries following spiking at the limit of quantitation were less than 20%. The values obtained are indicative of the method having good repeatability.
Reproducibility	An independent laboratory method validation (ILV) indicated that recoveries of pyraclostrobin and BF 500-3 were acceptable for grapes at the LOQ (0.02 ppm) and 100× LOQ (2.0 ppm) while recoveries for these analytes were low and variable for wheat straw. Incorporation of a 10-fold dilution to the standards and the control wheat straw samples spiked at the LOQ eliminated the interferences and resulted in acceptable recoveries of pyraclostrobin and BF 500-3. Overall, the Method D9808 was reproducible.	The independent laboratory method validation (ILV) demonstrated that acceptable recoveries were obtained with the first attempt for pyraclostrobin and the desmethoxy metabolite BF 500-3 in grapes and wheat straw at spiking levels of 0.02 ppm and 2.0 ppm, indicative of the method having good reproducibility.
Linearity	The method/detector response was linear within the range of 0.5–5.0 ng/μL for BAS 500 F (correlation coefficient r > 0.986) and BF 500-3 (correlation coefficient r > 0.991).	The method/detector response was linear within the range of 2–20 ng/μL for BAS 500 F (correlation coefficient r = 0.99961) and BF 500-3 (correlation coefficient r = 0.99953).
Specificity	The control chromatograms generally had no peaks above the chromatographic background and the spiked sample chromatograms contained only the analyte peak. The peak was well defined and symmetrical. There appeared to be no carryover to the following chromatograms.	The control chromatograms generally had no peaks above the chromatographic background and the spiked sample chromatograms contained only the analyte peak.

RESIDUE ANALYTICAL METHODS	ANIMAL MATRICES		
	HPLC Method 439/0	LC/MS/MS Method 446/1	LC/MS/MS Method D9902
Method ID	Validation of Analytical Method No. 439/0 for the determination of BAS 500F (As Parent Compound) in Matrices of Animal Origin	LC/MS/MS Method for Determination of Reg. No. 304428 (BAS 500F) and its Metabolites (BF 500-10) in Matrices of Animal Origin	Method Validation of BASF Analytical Method D9902, "Method for the Determination of Residues of BAS 500F and Its Metabolite BF 500-16 in Hen Tissues Using LC/MS/MS"
Analytes	Pyraclostrobin	Pyraclostrobin and the metabolites BF 500-5 and BF 500-8 in milk and tissues	Pyraclostrobin and the metabolites BF 500-5 and BF 500-9 in eggs and poultry tissues
Instrument	Kontron Autosampler 460	Autosampler: PE Series 200 Pump: HP 1100 Series Bin Pump HPLC-MS/MS system: 300	**Egg, liver and fat** PE Sciex API 3000 Biomolecular Mass Analyser
			Muscle PE Sciex API 3000 Triple Quadrupole Mass Spectrometer

Instrument parameters	Injection volume: 50 μL Mobile phase Pre-column [Isocratic elution] Solvent A: Iso-octane:MeOH: Iso-propanol 99:0.5:0.5 25 μL/H_2O distilled Analytical column [Column wash] Solvent B: Iso-octane:MeOH: Iso-propanol 90:5:5 25 μL/H_2O distilled Column switching: 11.5–13.0 min Flow rate: 1.0 mL/min for both columns Detector wavelength: 270 nm	Injection volume: 10 μL Mobile phase A: H_2O:ACN:Formic acid 900:100:1 Mobile phase B: H_2O:ACN:Formic acid 100:900:1 Gradient profile time (min.) % Solution B 0–5 isocratic 50% 5.0–5.1 linear 100% 5.1–7 isocratic 100% 7–7.1 linear 0% 7.1–10 isocratic 0% Flow rate: 0.25 mL/minute MS/MS Conditions: Scan type: MRM Ionisation: Turbo ion spray 8 L/minute N_2, 380°C Polarity: Positive Acquisition mode: Profile Transitions: BF 500-5 195 → 153 BF 500-8 211 → 194	**Egg, liver, fat and muscle** Inlet (HPLC System): PE 200 Micro Pump System + Perkin Elmer 200 Series Auto Sampler Injection volume: 10 μL (or higher) **Egg, liver and fat** Mobile phase Solution A: Water:4mM ammonium formate:0.1% formic acid (ratios not provided) Solution B: MeOH:4mM ammonium formate:0.1% formic acid (ratios not provided) Gradient profile Time (min.) % Solution A 0 70 1 30 3 30 8 70 8.1 70 Flow rate: 0.25 mL/minute **Muscle** Mobile phase Solution A: Water:0.1% formic acid (ratios not provided) Solution B: ACN:0.1% formic acid (ratios not provided) Gradient profile time (min.) % Solution A 0 90 2 50 2.1 50 9.1 0 11 90 Flow rate: 0.40 mL/minute

Instrument parameters (cont'd)			**Egg, liver, fat and muscle** Ionization Mode: Positive Transitions: BF 500-5 195 → 152.8 BF 500-9 211 → 169.3
Column	Pre-column: SiO_2 Material, Nucleosil 120 Si, 5 μ; Macherey & Nagel, 250*4.6 mm Analytical column: Al_2O_3-Material, Alox 60, 5 μ; 250*4.6mm	Prontosil 120-3, C30, 3 μm, 125 mm, D=3 mm	**Egg, liver and fat** Metachem Inertsil 3 μm ODS3, 50 mm × 2.1 mm
			Muscle Bischoff Prontosil 120–3 μm C30, 125 mm × 3.0 mm
Standardization method	An external standard method was used as marker for retention time, response and calibration	An external standard method was used as marker for retention time, response and calibration	An external standard method was used as marker for retention time, response and calibration
Stability of primary and(or) secondary standard solutions	Storage conditions not provided	Study states that fresh standard solutions be prepared every 3 months.	No decomposition of BAS 500F, BF 500-16, BF 500-5 and BF 500-9 occurred for 120 days when standard solutions were made in acetone or methanol, kept in amber bottles with Teflon-lined screw caps and stored in the refrigerator.
Retention times of ROC	BAS 500F = ~17 minutes	BF 500-5 = ~2.95 minutes BF 500-8 = ~3.66 minutes	**Egg, liver and fat** BF 500-5 = ~4.4 minutes BF 500-9 = ~3.6 minutes
			Muscle BF 500-5 = ~6.0 minutes BF 500-9 = ~4.4 minutes
Limit of detection (LOD)	0.025 μg/mL	2.5 ng/mL	2.5 pg/μL
Limit of quantitation (LOQ)	Milk: 0.01 mg/kg Eggs and tissues: 0.05 mg/kg	Milk: 0.01 mg/kg/analyte Tissues: 0.05 mg/kg/analyte	0.05 mg/kg/analyte

Repeatability	The relative standard deviations measured with respect to recoveries following spiking of BAS 500 F at the limits of quantitation (0.01 ppm and 0.05 ppm) were less than 12% in milk, less than 6% in muscle, liver, kidney and fat and less than 13% in eggs. The values obtained are indicative of the method having good repeatability.	The relative standard deviations measured with respect to recoveries following spiking of BAS 500 F and BF 500-10 at the limits of quantitation (0.01 ppm and 0.05 ppm) were less than 7% in milk and less than 5% in muscle, liver, kidney and fat. The values obtained are indicative of the method having good repeatability.	The relative standard deviations measured with respect to recoveries following spiking of BAS 500 F at the limit of quantitation (0.01 ppm) did not exceed 16% for egg, muscle and fat but reached 32% for liver. When spiked with BF 500-16 at the LOQ, relative standard deviations were below 18% for all poultry matrices. The values obtained are indicative of the method having good repeatability for the parent and the metabolite BF 500-16 in all matrices except liver.
Reproducibility	The independent laboratory method validation (ILV) demonstrated that acceptable recoveries were obtained with the first attempt for pyraclostrobin in milk and muscle at spiking levels equivalent to the LOQ and 10× LOQ, indicative of the method having good reliability and reproducibility.	An independent laboratory method validation (ILV) indicated that, although acceptable validation recoveries were attained with the first attempt for pyraclostrobin and BF 500-10 in milk at both spiking levels (0.01 ppm and 0.1 ppm), recoveries for liver were unacceptable due to matrix interference. Only when incorporating a dilution of the spiked liver sample, were recoveries deemed acceptable with better peak shapes and less interference. Overall, the Method LC/MS/MS 446/1 was deemed to be reproducible.	An independent laboratory method validation (ILV) was not conducted, on the basis that this method was very similar to the LC/MS/MS Method 446/1. However, given the difficulties encountered by the ILV for the LC/MS/MS Method 446/1, an ILV for this method should be submitted.
Linearity	The method/detector response was linear within the range of 1.25–20 ng for BAS 500 F (correlation coefficient r > 0.99).	No chromatograms of standards were provided and subsequently no standard curve was generated. Therefore, the linearity of the method could not be determined.	The method/detector response was linear within the range of 25–250 pg for both BF 500-5 (correlation coefficient r = 0.999) and BF 500-9 (correlation coefficient r = 0.996).
Specificity	The control chromatograms of milk, muscle, fat and eggs generally had no peaks above the chromatographic background while the control chromatograms of liver and kidney had peaks above background, indicating potential matrix interference. The spiked sample chromatograms contained only the analyte peak. The peak was well defined and symmetrical.	The control chromatograms of milk, muscle, fat, liver and kidney generally had no peaks above the chromatographic background. The spiked sample chromatograms contained only the analyte peak. The peak was well defined and symmetrical.	The spiked sample chromatograms indicated that the analytical peak was not totally symmetrical due to shouldering.

MULTIRESIDUE METHOD	Existing multiresidue methods of analysis which are currently in common usage were found to be suitable for the determination of pyraclostrobin but unsuitable for the determination of BF 500-3 in grape and peanut. Therefore, they were determined to be unsuitable as enforcement methods.

STORAGE STABILITY DATA	
Plant matrices	Residues of pyraclostrobin and the desmethoxy metabolite (BF 500-3) were stable at <-10°C for at least 19 months in/on spiked samples of peanut nutmeat, processed oil, grape juice, sugar beet tops and roots, tomatoes and wheat grain and straw. Since the freezer storage had no apparent impact on the stability of the residues of pyraclostrobin and the desmethoxy metabolite (BF 500-3) in plant matrices, the residue of concern (ROC) will not have to be redefined to account for residue degradation as a function of time.
Animal matrices	The submitted interim storage stability data, indicating that residues of pyraclostrobin and the metabolite BF 500-10 are stable under frozen storage conditions (-20°C) in/on spiked samples of cow milk, liver and muscle for up to 90 days (~3 months), are adequate to support the storage conditions and intervals of the whole and skim milk samples from the ruminant feeding study. The submitted storage stability data indicated that residues of pyraclostrobin and the metabolite BF 500-16 are stable under frozen storage conditions (<-10°C) in/on spiked samples of eggs for up to 7 months. The submitted storage stability data for eggs are adequate to support the storage conditions and intervals of the egg samples from the poultry metabolism and feeding studies while the submitted storage stability data for ruminant liver is translatable and adequate to support the storage conditions and intervals of the poultry liver samples from the metabolism and feeding studies. Tissue samples from the animal metabolism and feeding studies were stored for intervals greater than the time periods studied. Therefore, additional storage stability data are required to support the storage conditions and intervals of the milk fat, ruminant and poultry tissue samples. When the final report of the ruminant storage stability study becomes available, the stability of pyraclostrobin, BF 500-10 and BF 500-16 in milk fat, cow and poultry tissues stored under the conditions and intervals of the metabolism and feeding studies will be reassessed.

CROP FIELD TRIALS ***Root Vegetables (Except Sugar Beet)— Crop Subgroup 1-B:*** *Carrot and Radish*	The combined residues of pyraclostrobin and the metabolite BF 500-3 in/on carrots and radish roots harvested immediately (0-day PHI) following the last of three foliar applications (672–706 g a.i./ha/season; ~ 1× the maximum proposed seasonal rate) ranged from <0.04 to <0.33 ppm. The number of trials conducted in representative zones (1A, 5 and 5B) was insufficient. Nonetheless, based on the 0-day PHI and the potato metabolism study, zonal and climatic effects are not likely to have a significant impact on the magnitude of the residues (MORs). Consequently, additional trials for carrots and radishes will not be required. The proposed use on the Root and Tuber Vegetables (Except Sugar Beets) can be supported.
Tuberous and Corm Vegetable— Crop Subgroup 1-C *Potato*	When treated at ~0.7–1.0× proposed GAP (896–1389 g a.i./ha/season, 3-day PHI), the combined residues of pyraclostrobin and the metabolite BF 500-3 were <0.04 ppm (below the LOQ) in/on all samples of potatoes grown in the U.S. and Canada. Although the number of trials conducted in the required growing regions (as per Regulatory Directive DIR98-02) was insufficient, the available field trial data demonstrated that total residues were consistently below the method LOQ (0.04 ppm) within a zone and from one zone to another, therefore additional trials will not be required. The proposed use on the Tuberous and Corm Vegetables crop group can be supported.
Sugar Beet	The combined residues of pyraclostrobin and the metabolite BF 500-3 in/on sugar beet roots treated according to the proposed GAP (900 g a.i./ha/season, 7-day PHI) ranged from <0.04 to 0.15 ppm. The number of trials conducted in the required growing regions was insufficient, however, since large-scale blending and mixing of sugar beets grown over a wide geographic area occurs when processing sugar beets to sugar and molasses, the additional trials in growing regions 7A and 14 can be waived. Therefore, the use on sugar beets can be supported
Bulb Vegetables *Dry Bulb and Green Onion*	The combined residues of pyraclostrobin and BF 500-3 in/on dry bulb and green onions treated at 2× the recommended GAP (~500 g a.i./ha/season, 7-day PHI) ranged from <0.04 to 0.65 ppm, hence overestimating the residues at the proposed GAP. Furthermore, the number of supervised residue trials in the required growing regions was insufficient and the residue levels were inconsistent within each zone and from one zone to another. Therefore, the use on the Bulb Vegetables crop group can only be supported on a temporary basis, pending the submission of additional supervised residue trials conducted according to GAP in the representative growing regions (5 and 5B).
Dried Shelled Pea and Bean (Except Soybean)— Subgroup 6C: *Pea, (dry seed), lentil and bean (dry and snap)*	The supervised residue trials conducted on dry field peas, lentils and bean (dry and snap) grown in the U.S. (zone 5) and Canada (zones 7and 14), indicated that when treated at ~2.3× the proposed GAP (200–300 g a.i./ha/season, 30-day PHI), combined residues of pyraclostrobin and the metabolite BF 500-3 ranged from <0.05 to 0.37 ppm in peas, <0.05–0.48 ppm in lentils, <0.04–0.21 ppm in dry beans and <0.04–0.19 ppm in snap beans. The residue field trials on dry field peas, lentils and dry beans were conducted at greater than twice the recommended maximum application rate, hence, overestimating the residues at the proposed GAP. In the absence of a proposed label for snap beans, the adequacy of the supervised residue trials cannot be assessed. Consequently, using a weight-of-evidence approach, the use on all crops within the Dried Shelled Pea and Bean (Except Soybean) - Crop Subgroup 6C, can only be supported on a temporary basis pending agreement to submit additional residue data.

Fruiting Vegetables (Except Cucurbits) *Pepper (Bell and Non-bell) and Tomato*	When harvested on the day (0-day PHI) of the last of six foliar applications (~1344 g a.i./ha/season equivalent to ~1.12× the proposed GAP), the combined residues of pyraclostrobin and the metabolite BF 500-3 in/on bell peppers, non-bell peppers and tomatoes were <0.04–<0.30 ppm, <0.14–0.99 ppm and <0.08–<0.25 ppm, respectively. The number of residue trials on fruiting vegetables in representative growing regions 5 and 5B was insufficient based on guidance in Regulatory Directive DIR98-02. Nonetheless, based on the 0-day PHI, zonal and climatic effects are not likely to have a significant impact on the magnitude of the residues (MORs). Additional residue trials for bell peppers, chili peppers and tomatoes will not be required. Therefore, the use on the Fruiting Vegetables crop group can be supported.
Cucurbit Vegetables: *Cucumber, Muskmelon (Cantaloupe), and Summer Squash*	The results of the cucurbit field trials indicated that the combined residues of pyraclostrobin and the metabolite BF 500-3 in/on cantaloupes, cucumbers and summer squash, treated at ~2.0× the maximum proposed seasonal application rate (672 g a.i./ha) and harvested immediately following the last application, were <0.08–0.16 ppm, <0.04–<0.43 ppm and <0.07–<0.22 ppm, respectively. The residue data on cucurbit vegetables were conducted at twice the recommended maximum application rate, hence overestimating the residues at the proposed GAP. Furthermore, the number of residue trials carried out in the required growing regions was insufficient, based on guidance in Regulatory Directive DIR98-02. Therefore, the use on the Cucurbit Vegetables crop group can only be supported on a temporary basis pending additional trials conducted according to GAP.
Citrus Fruits (Citrus Spp., Fortunella Spp.): *Grapefruit, lemons and oranges*	The combined residues of pyraclostrobin and the metabolite BF 500-3 ranged from <0.08 to 0.61 ppm in/on grapefruit, lemons and oranges treated according to the U.S. maximum proposed seasonal application rate (896 g a.i./ha) and harvested 13–14 days following the last application. Separate analyses of the citrus pulp and peel samples indicated that combined residues were <0.04 ppm and <0.08–0.54 ppm, respectively.
Stone Fruits: *Cherry (Sweet and Tart), Peach, and Plum*	The combined residues of pyraclostrobin and the metabolite BF 500-3 in/on cherries (sweet and tart), peaches and plums, treated at 1.0× the proposed GAP (~670 g a.i./ha/season) and harvested immediately (0-day PHI) following the last application, were <0.27–<0.44 ppm in/on sweet cherries, 0.45–0.67 ppm in/on tart cherries, <0.09–<0.33 ppm in/on peaches and <0.04–<0.21 ppm in/on plums. The number of residue trials conducted in the required growing regions was insufficient based on guidance in Regulatory Directive DIR98-02. Furthermore, according to the Occupational Exposure Assessment Section's review, the 0-day PHI cannot be supported. Moreover, a 10-day re-entry interval (REI) for thinning, pruning and hand harvesting of stone fruits was recommended. Based on these observations, the use on the Stone Fruits crop group can only be supported on a temporary basis. Additional trials conducted according to the proposed label directions may be required to support the use, pending the outcome of the Occupational Exposure Assessment Section's review of the requested dermal absorption study and the Fungicide/Herbicide Toxicology Evaluation Section's assessment of the requested toxicology data.

Berries: *Blueberry and Raspberry*	The combined residues of pyraclostrobin and the metabolite BF 500-3 were <0.12–0.69 ppm in/on highbush blueberries and <0.46–0.97 ppm in/on red raspberries harvested immediately (0-day PHI) following the last of four foliar applications (806 g a.i./ha; ~ 1.0× the maximum proposed seasonal application rate). The residue data was inadequate based on the insufficient number of trials conducted in the required growing regions. Furthermore, among the crops within the Berries crop group, the efficacy data supports only the use on the Bushberry subgroup 13B. The occupational exposure data supports the use on lowbush and highbush blueberries provided the REIs for hand harvesting are increased to 24 hours and 29 days, respectively. Based on these observations, the use on the Berries crop group can only be supported on a temporary basis. Additional trials conducted according to the proposed label directions for blueberries and raspberries may be required pending the outcome of the Occupational Exposure Assessment Section's review of the requested dermal absorption study, the Fungicide/Herbicide Toxicology Evaluation Section's assessment of the requested toxicology data and the review of additional efficacy data on raspberries (Caneberry crop subgroup 13A).

Tree Nuts: *Almond and Pecan nutmeat*	The combined residues of pyraclostrobin and the metabolite BF 500-3 in/on almonds and pecans treated according to the U.S. maximum proposed seasonal application rate (538 g a.i./ha, 14-day PHI) were <0.04 ppm in/on all samples of nutmeat.
Pistachios:	The combined residues of pyraclostrobin and the metabolite BF 500-3 in/on pistachios treated according to the U.S. maximum proposed seasonal application rate (896 g a.i./ha, 14-day PHI) were <0.04–0.48 ppm.
Small Grains: *Barley*	The combined residues of pyraclostrobin and BF 500-3 in/on barley hay harvested 9–16 days and barley grain and straw harvested 38–70 days following treatment at ~1.8× GAP (300 g a.i./ha/season) were 1.06–25 ppm (U.S.) and 0.80–5.51 ppm (Canada) in/on barley hay, <0.04–0.19 ppm (U.S.) and <0.04–0.33 ppm (Canada) in/on barley grain and <0.04–3.17 ppm (U.S.) and 0.26–5.55 ppm (Canada) in/on barley straw. A higher variability in barley hay residue levels was observed in the samples collected from the U.S. trials.
Rye	The combined residues of pyraclostrobin and the metabolite BF 500-3 in/on rye grain harvested 55–66 days following treatment at ~1.5× proposed GAP (300 g a.i./ha/season) were <0.04 ppm.
Wheat	The efficacy review concluded that the fusarium head blight (FHB) control claim on the Headline EC label is not supported. Therefore, as the data for the late treatment schedule was deemed inadequate, only the data pertaining to the early season applications were reviewed. The combined residues of pyraclostrobin and the metabolite BF 500-3 were consistent, ranging from <0.04 to <0.05 ppm in/on wheat grain grown in the U.S. and in Canada and treated at ~1.6× proposed GAP (300 g a.i./ha/season). Although the supervised residue trials on cereal grains were conducted at higher rates than proposed on the label, the residue data for each cereal grain was consistent within each zone and from one zone to another.
Small grains—European trials:	The submitted European field trial data indicated that combined residues of pyraclostrobin and the metabolite BF 500-3 ranged from <0.04–0.15 ppm in/on barley and wheat grain harvested at maturity following treatment with formulations. This data demonstrated that combined residues of pyraclostrobin and BF 500-3 are relatively similar with the residue levels observed in the cereal grain (<0.04–0.33 ppm) collected from field trials conducted in Canada and the U.S..
Banana:	The trials were conducted in the major banana-growing regions of Central and South America. The combined residues of pyraclostrobin and the metabolite BF 500-3 were <0.04 ppm in/on all samples of bagged or unbagged bananas (whole fruit including peel), harvested immediately (0-day PHI) following treatment at ~2.5× the proposed seasonal maximum application rate. Although the trials provided were conducted at higher rates, residues were consistently below the LOQ (0.04 ppm) from one zone to another and within each zone.

Peanut:	The combined residues of pyraclostrobin and the metabolite BF 500-3 in/on peanut nutmeat harvested 14–18 days following the last of five foliar applications (1389–1434 g a.i./ha/season; ~1× the U.S. maximum proposed seasonal application rate) were <0.04–<0.045 ppm.
Strawberry:	The combined residues of pyraclostrobin and the metabolite BF 500-3 in/on strawberries harvested immediately (0-day PHI) or one day following treatment at GAP (~1000 g a.i./ha/season) were <0.07–<0.39 ppm. The number of residue trials on strawberries in representative growing regions 5 and 5B was insufficient based on guidance in Regulatory Directive DIR98-02. Nonetheless, based on the 0-day PHI, zonal and climatic effects are not likely to have a significant impact on the magnitude of the residues (MORs). Hence, additional residue trials will not be required and the use on strawberries can be supported. Trials conducted on tomatoes, cucurbits (cantaloupes, cucumbers and summer squash), citrus fruits (grapefruits, lemons and oranges), stone fruits (cherries, peaches and plums), tree nuts (almonds and pecans), pistachios and grapes using dilute and concentrate spray volumes indicated that higher residues were not likely to result from either type of application.
RESIDUE DECLINE	The residue decline studies on carrot, sugar beet (tops), onion (dry bulb), snap bean, tomato, cucumber, peach, plum, raspberry, grape, peanut (hay) and strawberry indicated that combined residues of pyraclostrobin and BF 500-3 decreased gradually at longer post-treatment intervals. The residue decline data for sugar beet (root), dry field pea seed, lentil seed, dry bean, almond (hulls), barley and wheat (hay, grain and straw) and peanut (nutmeat) did not demonstrate any conclusive trends in decreasing pyraclostrobin residues at longer post-treatment intervals.

PROCESSED FOOD/FEED	
Citrus Fruits:	No concentration of residues of pyraclostrobin and BF 500-3 was observed in juice processed from oranges bearing detectable residues. However, the combined residues of pyraclostrobin and the metabolite BF 500-3 concentrated in dried pulp (8.2–9.5×) and in oil (5.3–6.8×) resulting in maximum expected combined residues of 5.16 ppm and 3.54 ppm, respectively.
Peanut:	No concentration of residues of pyraclostrobin and BF 500-3 was observed in peanut meal processed from peanut nutmeat bearing detectable residues. The data indicated that the combined residues of pyraclostrobin and the metabolite BF 500-3 concentrated in peanut oil (1.6× and 2.2×). Therefore, the maximum expected pyraclostrobin and BF 500-3 residues in peanut oil would be 0.081 ppm.
Plum:	The residues of pyraclostrobin and the metabolite BF 500-3 concentrated slightly in prunes (1.2× and 1.3×), therefore, the maximum expected combined residues would be 0.273 ppm.
Potato:	The submitted potato processing data indicated that the combined residues of pyraclostrobin and the metabolite BF 500-3 were below the LOQ (<0.04 ppm) in/on potato samples following treatment at 5× the maximum proposed rate. Therefore, no potato processing study was required.
Sugar Beet:	The submitted sugar beet processing data indicated no concentration of residues of pyraclostrobin and BF 500-3 in molasses and refined sugar processed from sugar beets bearing detectable residues.
Tomato:	No concentration of residues of pyraclostrobin and BF 500-3 was observed in tomato puree. However, combined residues concentrated in tomato paste (1.5× and 2.6×) when processed from whole tomatoes bearing detectable residues. The maximum expected pyraclostrobin and BF 500-3 residues in tomato paste would be 0.494 ppm.
Wheat:	The submitted wheat processing data indicated that no concentration of residues of pyraclostrobin and BF 500-3 was observed in flour, bran, middlings, shorts, and germ processed from wheat grain bearing detectable residues. The combined residues of pyraclostrobin and the metabolite BF 500-3 were <0.067–0.445 ppm in/on aspirated grain fractions from wheat treated at the earlier application schedule.
DAIRY CATTLE FEEDING	Dairy cows were orally dosed twice daily for 28 consecutive days with pyraclostrobin at dose levels equivalent to 8.8 ppm, 27.2 ppm (mid dose), and 89.6 ppm (high dose), corresponding to ≈0.25×, ≈0.75×, and 2.5× the maximum theoretical dietary burdens (MTDB) of pyraclostrobin for beef (36.3 ppm) and dairy (35.4 ppm) cattle. Overall, residues of pyraclostrobin increased in milk and tissues with the increase in the dose level. Residues in whole milk appeared to plateau at day 15 and did not significantly increase with subsequent doses. Maximum combined residues of pyraclostrobin and the metabolites hydrolyzable to BF 500-5 and BF 500-8 were highest in liver, followed by kidney, milk fat, whole milk, skim milk, fat and muscle. The depletion study (cows sacrificed 2 and 7 days following withdrawal from treatment) demonstrated that residues declined in milk and tissues once exposure was discontinued.

POULTRY FEEDING	Laying hens were orally dosed once daily for 30 consecutive days with pyraclostrobin at dose levels equivalent to 0.28 ppm, 0.88 ppm, and 3.01 ppm (8.6× the MTDB of pyraclostrobin for poultry of 0.35 ppm). At the highest feeding level, residues of pyraclostrobin, the metabolites hydrolyzable to BF 500-5 and an isomeric compound (BF 500-9) were less than the method LOQ (0.05 ppm) in all egg and tissue samples. Residue analysis of BF 500-8 was not conducted (the metabolism data showed all metabolites hydrolyzable to BF 500-8 would be less than 10% TRR). Samples from the low and mid dose groups, and depletion samples from the high dose group were not analyzed. The poultry metabolism studies were conducted at doses equivalent to 35–36× the MTDB. When extrapolated to the 1× burden, the TRRs in eggs, fat and liver would be at least 3 times below 0.05 ppm, which is the LOQ for BF 500-5 or BF 500-8. Therefore, residue limits for eggs and poultry tissues will not be established.
CONFINED ROTATIONAL CROPS	In the RACs of radishes, lettuce and wheat planted 30, 120 and 365 days following soil treatment with [chlorophenyl-^{14}C]pyraclostrobin or [tolyl-^{14}C]pyraclostrobin at total application rates for each label of 896 g a.i./ha or 1456 g a.i./ha , TRRs (expressed as pyraclostrobin equivalents) accumulated at levels >0.01 ppm in samples of radish roots and tops, head lettuce and wheat forage, straw and grain planted 30 days after treatment (DAT), 120-DAT radish tops, head lettuce and wheat forage, straw and grain and 365-DAT radish roots and tops, head lettuce and wheat forage straw, and grain. Pyraclostrobin and the desmethoxy metabolite BF 500-3 were identified in 30-DAT rotational crop commodities except head lettuce and wheat grain, in 120-DAT wheat forage and straw and in 365-DAT wheat forage and straw. Because TRR levels were low, additional extractable residues were characterized as polar, medium polar, or non-polar fractions. Overall the study indicated that metabolism of pyraclostrobin in rotated crops is similar to that in primary crops, with pyraclostrobin undergoing demethoxylation to yield BF 500-3, followed by further degradation to medium polar and polar metabolites and subsequent conjugation reactions and incorporation into natural products (cellulose and lignin in all rotational crop commodities and starch in wheat grain). Provided the information confirming that rotational crop samples were analyzed within the interval represented by the storage stability study is submitted, the confined rotational crop study was conditionally accepted. The confined crop rotation study supports the definition of the residue of concern (ROC), pyraclostrobin and the desmethoxy metabolite BF 500-3, as defined in the plant metabolism studies.
FIELD ACCUMULATION—ROTATIONAL CROPS	Residues of pyraclostrobin and the metabolite BF 500-3 were each less than the method LOQ (<0.02 ppm) in/on rotational crop matrices (radish, roots and tops; cabbage, with and without wrapper leaves; and wheat forage, hay, straw and grain) planted 14 days following the last of six sequential foliar applications to the primary crop, cucumbers, at 0.21–0.22 kg a.i./ha/application (~1× the maximum proposed seasonal rate for annual crops). The study was adequate, however, a 14-day plant-back interval (PBI) restriction for all crops that are not on either the Headline EC or Cabrio EG labels is required.

PROPOSED MRLs	Dried shelled pea and bean (except soybean) (Crop Subgroup 6C: bean (adzuki, broad dry, dry, kidney, lablab, lima dry, moth, mung, navy, pink, pinto, rice, tepary, urd), catjang, chick pea, cowpea, guar, lentil, lupin (grain, sweet) and pea (blackeyed, crowder, field, field seed, pigeon and southern))	0.5 ppm
	Tuberous and corm vegetables (Crop Subgroup 1C: arracacha, arrowroot, artichoke (chinese, Jerusalem), canna (edible), cassava, chayote root, chufa, dasheen, ginger, leren, potato, sweet potato, tanier, turmeric and yam (bean, true))	0.04
	Sugar beets	0.15
	Barley	0.4
	Wheat	0.2
	Rye	0.04
	Root vegetables (Crop Subgroup 1B: beet (garden), burdock (edible), carrot, celeriac, chervil (turnip rooted), chicory root, ginseng, horseradish, parsley (turnip rooted), parsnip, radish (oriental), rutabaga, salsify (black, spanish), skirret and turnip)	0.4
	Bulb vegetables (Crop Group 3: garlic (great headed), leek, onion (dry bulb, green, potato, tree, Welsh) and shallot)	0.65
	Fruiting vegetables (Crop Group 8: chili, eggplant, groundcherry, pepino, pepper (bell, non-bell, non-bell sweet), tomatillo and tomato)	1.0
	Cucurbit vegetables (Crop Group 9: balsam apple, balsam pear, cantaloupe, chayote, cucumber (chinese), gherkin (West Indian), gourd (edible), melon (citron), muskmelon, pumpkin, squash (summer, winter), watermelon and waxgourd (chinese))	0.5
	Stone fruits (Crop Group 12: apricot, cherry (sweet, tart), nectarine, peach and plum (chickasaw, damson, Japanese, prune, fresh prune))	0.7
	Berries (Crop Group 13: blackberry, blueberry, caneberry, currant, elderberry, gooseberry, huckleberry, loganberry and raspberry)	1.0
	Strawberry	0.4
	Grapes	2.0
	Raisins	7.0
	Fat and meat of cattle, goats, hogs, horses and sheep	0.1
	Meat by-products except liver of cattle, goats, hogs, horses and sheep	0.2
	Liver of cattle, goats, hogs, horses and sheep	1.5
	Milk	0.1
PROPOSED IMPORT TOLERANCES	Banana	0.04
	Citrus Fruits (Crop Group 10: calamondin, citron, citrus hybrids, grapefruit, kumquat, lemon, lime, mandarin (satsuma), orange (sour, sweet), pummelo, tangelo and tangerine)	0.7
	Citrus, oil	4.0
	Tree Nuts (Crop Group 14 which includes almond, beechnut, butternut, cashew, chestnut, chinquapin, filbert, nut (brazil, hickory, macadamia), pecan and walnut)	0.04
	Peanut	0.05
	Peanut, refined oil	0.1
	Pistachio	0.5

U.S. TOLERANCES **** U.S. crop groups and subgroups with their corresponding crops are defined under** www.epa.gov/opphed01/foodfeed/index.htm*	Almond hulls	1.6 ppm
	Banana	0.04
	Barley, grain	0.4
	Barley, hay	25
	Barley, straw	6.0
	Bean, dry	0.3
	Beet, sugar, dried pulp	1.0
	Beet, sugar, roots	0.2
	Beet, sugar, tops	8.0
	Berry group	1.3
	Citrus, dried pulp	5.5
	Citrus, oil	4.0
	Fruit, citrus, group	0.7
	Fruit, stone, group	0.9
	Grain, aspirated fractions	2.5
	Grape	2.0
	Grape, raisin	7.0
	Grass, forage	10
	Grass, hay	4.5
	Grass, seed screenings	27
	Grass, straw grown for seed	14
	Nut, tree group	0.04
	Peanut	0.05
	Peanut, refined oil	0.1
	Pistachio	0.7
	Radish, tops	16
	Rye, grain	0.04
	Rye, straw	0.5
	Strawberry	0.4
	Vegetable, bulb	0.9
	Vegetable, cucurbit, group	0.5
	Vegetable, fruiting, group	1.4
	Vegetable, root, except sugarbeet, subgroup	0.4
	Vegetable, tuberous and corm, subgroup	0.04
	Wheat, grain	0.02
	Wheat, hay	6.0
	Wheat, straw	8.5
	Fat and meat of cattle, goats, hogs, horses and sheep	0.1
	Meat by-products except of cattle, goats, hogs, horses and sheep	0.2
	Liver of cattle, goats, hogs, horses and sheep	1.5
	Milk	0.1
CODEX MRLs	No Codex CXLs are currently established	
DIETARY RISK ASSESSMENT (DRA) *DEEM™ Version 7.72* *1994–1998 Continuing Survey of Food Intakes by Individuals* *Interim ADI = 0.003 mg/kg bw/d*	It was estimated that the chronic dietary exposure to pyraclostrobin from food and water represented approximately 35% of the interim ADI for children 1–6 years old. The PDI for the remaining population subgroups, including infants, children, adults and seniors, each represented <24 % of the interim ADI. Consequently, the consumption estimates coupled with the proposed MRLs indicate that there is adequate protection of the consumer, including infants, children, adults and seniors, from dietary exposure to residues of pyraclostrobin.	

Appendix IV Environmental assessment

Table 1 Fate and behaviour in the terrestrial environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	pyraclostrobin	did not hydrolyse at pH 5, pH 7 and pH 9	not an important route of transformation in the environment
Phototransformation on soil	pyraclostrobin	half-life dark: 24–41 day irradiated: 33–44 day	not an important route of transformation in the environment
Phototransformation in air	pyraclostrobin	not required—not volatile	
Biotransformation			
Biotransformation in aerobic soil	pyraclostrobin	half-life: 82–277 day DT$_{50}$: 14–270 day DT$_{75}$: 40–>365 day DT$_{90}$: 121–>365 day	BF 500-3 and BF 500-6 was the major transformation product biphasic transformation moderately persistent to persistent
Biotransformation in anaerobic soil	pyraclostrobin	half-life: 3 day DT$_{90}$: 6–10 day	BF 500-3, BF 500-4, and 500M75 major transformation products non-persistent
Mobility			
Adsorption/ desorption in soil	pyraclostrobin	adsorption K$_{oc}$: >5000	immobile
	BF 500-3	adsorption K$_{oc}$: 4240–>5000	slightly mobile to immobile
	BF 500-5	adsorption K$_{oc}$: 340–1163	low to moderate mobility
Volatilization	pyraclostrobin	not volatile	

Property	Test substance	Value		Comments
Field studies				
Field dissipation (Canadian and Canadian equivalent U.S. sites)	(Headline EC, Cabrio EG)	DT_{50}	15–48 day	biphasic dissipation
		DT_{75}	30–320 day	BF 500-6 as the major transformation product.
		DT_{90}	110–>365 day	Minor transformation products were BF 500-3, BF 500-5, BF 500-7
Field leaching	Headline EC, Cabrio EG	parent and transformation products were detected primarily in the top 0–15 cm soil layer		low potential leaching

Table 2 Fate and behaviour in the aquatic environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis	pyraclostrobin	did not hydrolyze at pH 5, pH 7 and pH 9	not an important route of transformation in the environment
Phototransformation in water	pyraclostrobin	half-life: < 2 h	indirect photolysis may be an important route of transformation
Biotransformation			
Biotransformation in aerobic water- sediment systems	pyraclostrobin	Supplemental study for aerobic water biotransformation data requirement	Require an aerobic water-sediment study

Table 3 Maximum EEC in vegetation and insects after a direct over-spray of Headline EC

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/dry weight ratios	EEC (mg a.i./kg dw)
Short range grass	289	3.3[b]	953
Leaves and leafy crops	151	11[b]	1663
Long grass	132	4.4[b]	582
Forage crops	162	5.4[b]	875
Small insects	70	3.8[c]	267
Pods with seeds	15	3.9[c]	56
Large insects	12	3.8[c]	46
Grain and seeds	12	3.8[c]	46
Fruit	18.1	7.6[c]	138

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994)

[b] Fresh/dry weight ratios from Harris (1975)

[c] Fresh/dry weight ratios from Spector (1956)

Table 4 Maximum EEC in vegetation and insects after a direct over-spray of Cabrio EG

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/dry weight ratios	EEC (mg a.i./kg dw)
Short range grass	257	3.3[b]	848
Leaves and leafy crops	134	11[b]	1478
Long grass	118	4.4[b]	517
Forage crops	144	5.4[b]	778
Small insects	62	3.8[c]	237
Pods with seeds	13	3.9[c]	50
Large insects	11	3.8[c]	41
Grain and seeds	11	3.8[c]	41
Fruit	16.1	7.6[c]	122

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994)

[b] Fresh/dry weight ratios from Harris (1975)

[c] Fresh/dry weight ratios from Spector (1956)

Table 5 Maximum EEC in diets of birds and mammals—Headline EC and Cabrio EG

Organism	Matrix	EEC (mg a.i./kg dw diet)	
		Headline EC	Cabrio EG
Bobwhite quail	30% small insects 15% forage crops 55% grain	236.4	210.1
Mallard duck	30% large insects 70% grain	45.7	40.6
Rat	70% short grass 20% grain/seeds 10% large insects	681.1	605.4
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	676.9	601.8

Table 6 Effects on terrestrial organisms—summary

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Invertebrates				
Earthworm	Acute	BAS 500 F	14-d LC_{50} = 567 mg a.i./kg soil 14-d NOEC = 151 mg a.i./kg soil	no classification
Bee	Contact	BAS 500 F	48-h LD_{50} =>100 µg a.i./bee NOEC =>100 µg a.i./bee	relatively non-toxic (Atkins et al., 1982)
Predatory mites (*Typhlodromus pyri*)	Contact (field study)	BAS 500 00F (250 g a.i./L; EC) applied at 160–640 g a.i./ha	no endpoints were selected	harmless to low risk (BBA hazard rating)
	Contact (lab study)	BAS 500 00F (250 g a.i./L; EC) applied at 320 g a.i./ha	no endpoints were selected	moderately harmful based on the overall effect at 320 g a.i./ha (maximum proposed label rate is 225 g a.i./ha)

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Parasitic wasp (Aphidius rhopalosiphi)	Contact (lab study)	BAS 500 00F (250 g a.i./L; EC) applied at 320 g a.i./ha	no endpoints were selected	moderately harmful based on the overall effect
	Contact (barley seedling; greenhouse)	BAS 500 00F (250 g a.i./L; EC) applied at 320 g a.i./ha	no endpoints were selected	harmless based on the overall effect
Foliage dwelling predators lady bird beetle—(*Coccinella septempunctata*)	Contact (lab study)	BAS 500 00F (250 g a.i./L; EC) applied at 320 g a.i./ha	no endpoints were selected	highly toxic at 320 g a.i./ha based on high mortality (maximum proposed label rate is 225 g a.i./ha)
Foliage dwelling predators green lacewing—(*Chrysoperla carnea*)	contact—reproduction dried residues	BAS 500 00F (250 g a.i./L; EC) applied at320 g a.i./ha	no endpoints were selected	harmless—slightly harmful based on the overall effect
Soil dwellers carabid beetle (*Poecilus cupreus*)	contact	BAS 500 00F (250 g a.i./L; EC) applied at320 g a.i./ha	no endpoints were selected	harmless
Soil dwellers wolf spiders (*Pardosa sp.)*	Contact	BAS 500 00F (250 g a.i./L; EC) applied at320 g a.i./ha	no endpoints were selected	harmless
Birds				
Bobwhite quail	Acute	BAS 500F	LD_{50} = >2000 mg a.i./kg bw NOEC = 500 mg a.i./kg bw	practically non-toxic (U.S. EPA)
	Dietary	BAS 500F	5d-LC_{50} =>5000 mg a.i./kg dw 5d-NOEC = 2500 mg a.i./kg dw	practically non-toxic (U.S.EPA)
	Reproduction	BAS 500F	NOAEC = 1062 mg a.i./kg dw	no classification

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Mallard duck	Dietary	BAS 500F	5d-LC_{50} =>5000 mg a.i./kg dw 5d-NOEC = 625 mg a.i./kg dw	practically non-toxic (U.S.EPA)
	Reproduction	BAS 500F	NOAEC = 1062 mg a.i./kg dw	no classification
Rat	Acute—oral	pyraclostrobin	LD_{50} >5000 mg a.i./kg bw	Low toxicity
		Headline EC	LD_{50}—260 mg Headline EC/kg bw	high toxicity
		Cabrio EG	LD_{50} > 2000 mg Cabrio EG/kg bw	Low toxicity
	Acute—dermal	pyraclostrobin	LD_{50} > 2000 mg a.i./kg bw	Low toxicity
		Headline EC	LD_{50} > 4000 mg Headline EC/kg bw	low toxicity
		Cabrio EG	LD_{50} > 2000 mg Cabrio EG/kg bw	Low toxicity
	90-d dietary	pyraclostrobin	LOAEL = 10.7/12.6 mg/kg bw/d (150 mg a.i./kg dw) NOAEL = 3.5/4.2 mg/kg bw/d (50 mg a.i./kg dw)	no classification

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
	2-yr dietary	pyraclostrobin	**Chronic Effects** Males: LOAEL = 9.2 mg/kg bw/d Females: LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 12.6 mg/kg bw/d. **Oncogenicity** No evidence of treatment-related oncogenicity.	MTD was not attained

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
	2 generation reproduction	pyraclostrobin	**Systemic Toxicity** LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 300 mg a.i./kg dw (29 kg bw/d for males and 30.4 mg/kg bw/d for females). **Reproductive Toxicity** LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 300 mg a.i./kg dw (29.0 mg/kg bw/d for males and 30.4 mg/kg bw/d for females). **Offspring Toxicity** LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 300 mg a.i./kg dw (29.0 mg/kg bw/d for males and 30.4 mg/kg bw/d for females).	MTD was not attained

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Mouse	90-d dietary	pyraclostrobin	**Males**: LOAEL = 30.4 mg/kg bw/d (150 mg a.i./kg dw) NOAEL = 9.2 mg/kg bw/d (50 mg a.i./kg dw) **Females:** LOAEL = 12.9 mg/kg bw/d (50 mg a.i./kg dw) NOAEL could not be determined since there were treatment-related effects observed at all dose levels tested.	
	80-week dietary	pyraclostrobin	LOAEL could not be determined since there were no adverse, treatment-related effects. NOAEL = 17.2/32.9 mg/kg bw/d. **Oncogenicity** No evidence of treatment-related oncogenicity.	MTD was not attained
Rabbit	skin irritation	pyraclostrobin	MAS 2.2/8.0 (maximum average score)	moderately irritating
		Headline EC	MAS = 4.33/8.0	severely irritating
		Cabrio EG	MAS = 1.2/8.0	slightly irritating

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
	teratogenicity (oral gavage)	pyraclostrobin	**Developmental/Maternal toxicity** NOAEL = 5 mg a.i./kg bw/d **Teratogenicity** Treatment related teratogenic effects were observed at 20 mg a.i./kg bw/d	no classification
Vascular plants				
Vascular plant	Seedling emergence	BAS 500 00F (23.6% a.i.)	21-d EC25 = >132 g a.i./ha 21-d NOEC = > 132 g a.i./ha	no classification
	Vegetative vigour	BAS 500 00F (23.6% a.i.)	21-d EC25 = >132 g a.i./ha 21-d NOEC = > 132 g a.i./ha	no classification

[a] Atkins et al. (1981) for bees and U.S. EPA classification for others, where applicable

Table 7 Effects on aquatic organisms—summary

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Freshwater species				
Daphnia magna	Acute	BAS 500 F	48-h EC$_{50}$ = 15.7 μg a.i./L 48-h NOEC = 11.5 μg a.i./L	very highly toxic
		BF 500-11	48-h EC$_{50}$ =>100 mg/L 48-h NOEC—100 mg/L	practically non-toxic
		BF 500-13	48-h EC$_{50}$=>100 mg/L 48-h NOEC = 50 mg/L	practically non-toxic
		BF 500-14	48-h EC$_{50}$— > 61.8 mg/L 48-h NOEC > 61.8 mg/L	slightly toxic

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
	Chronic	BAS 500 F	21-d NOEC = 4 µg a.i./L 21-d LOEC = 8 µg a.i./L	no classification
Rainbow trout	Acute	BAS 500 F	96-h $_{LC50}$ = 6.2 µg a.i./L 96-h NOEC = 3.6 µg a.i./L	very highly toxic
		BF 500-11	96-h LC_{50} = > 99.2 mg/L 96-h NOEC = 9.98 mg/L	practically non-toxic
		BF 500-13	96-h LC_{50} = 75 mg/L 96-h NOEC = 9.3 mg/L	slightly toxic
		BF 500-14	96-h LC_{50} = 57 mg/L 96-h NOEC = 39.4 mg/L	slightly toxic
	Chronic	BAS 500 F	98 d NOEC = 2.35 µg a.i./L LOEC = 6.42 µg a.i./L	no classification
Bluegill sunfish (juvenile)	Acute	BAS 500 F	96-h LC_{50}= 11.4 µg a.i./L 96-h NOEC = 6.08 µg a.i./L	very highly toxic
Freshwater alga/diatoms	Green algae—acute (*Pseudokirchneriella subcapitata*)	BAS 500 F	96-h NOEC = 14 µg a.i./L 96-h EC_{50} = 152 µg a.i./L,	no classification
	Blue green algae—acute (*Anabaena flos-aquae*)	BAS 500 F	120-h NOEC = 1.78 mg a.i./L 120-h EC_{50} = >1.78 mg a.i./L	
	Diatoms—acute (*Navicula pelliculosa*)	BAS 500 F	120-h NOEC = 1.18 µg a.i./L 120-h EC_{50} = 1.5 µg a.i./L	
	Green algae—acute (*Scenedesmus subspicatus*)	BF 500-11	72-h NOEC = 50 mg/L 72-h EC_{50} = 100 mg/L	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
	Green algae—acute (*Scenedesmus subspicatus*)	BF 500-13	72-h NOEC = 12.5 mg/L 72-h EC_{50} = 66 mg/L	
	Green algae—acute (*Scenedesmus subspicatus*)	BF 500-14	72-h NOEC = 12.5 mg/L 72-h EC_{50} = 47 mg/L	
Vascular plant (*Lemna gibba*)	Dissolved	BAS 500 F	14-day NOEC = 0.896 mg a.i./L 14-day EC_{50} = 1.72 mg a.i./L	no classification
	Over-spray	No data		
Marine species				
Crustacean (mysid shrimp)—juvenile	Acute	BAS 500 F	96-h LC_{50}= 4.16 μg a.i./L 96-h NOEC = 2.12 μg a.i./L	very highly toxic
Mollusk shell deposition	Acute	BAS 500 F	96-h EC_{50}=12.5 μg a.i./L NOEC = 4.1 μg a.i./L	very highly toxic
Sheepshead minnow	Acute	BAS 500 F	96-h LC_{50} = 76.9 μg a.i./L 96-h NOEC = 53.5 μg a.i./L	very highly toxic
	Chronic	BAS 500 F	36-d NOEC =10.8 μg a.i./L 36-d LOEC = 24 μg a.i./L	no classification
Fathead minnow	Chronic	BAS 500 F	NOEC = 4.14 μg a.i./L LOEC = 8.37 μg a.i./L	no classification
Marine algae	Acute (*Skeletonema costatum*)	BAS 500 F	120-h NOEC = 9.73 μg a.i./L 120-h EC_{50} = 65 μg a.i./L	no classification

[a] U.S. EPA classification, where applicable

Table 8 Risk to terrestrial organisms—Headline EC

Organism	Exposure	Endpoint value	EEC	MOS	Risk*
Invertebrates					
Earthworm	Acute	NOEC = 151 mg a.i./kg soil	0.57 mg a.i./kg soil	265	Negligible
Bee	Contact	NOEC =>112 kg a.i./ha	1350 g a.i./ha	83	Negligible
Birds					
Bobwhite quail	Acute	LD_{50} = 2000 mg a.i./kg bw NOEL = 500 mg a.i./kg bw	236 mg a.i./kg dw		It takes 92 d of pyraclostrobin intake to reach the LD_{50}. It takes 23 d of pyraclostrobin intake to reach the NOEL.
	Dietary	NOEC = 2500 mg a.i./kg dw	236 mg a.i./kg dw	11	Negligible
	Reproduction	NOAEC = 1062 mg a.i./kg dw	236 mg a.i./kg dw	4.5	Low
Mallard duck	Dietary	NOEC = 625 mg a.i./kg dw	45.7	14	Negligible
	Reproduction	NOAEC = 1062 mg a.i./kg dw	45.7	23	Negligible
Mammals					
Rat	Acute	LD_{50} = 5000 mg a.i./kg bw	681		43 d to reach the LD_{50}
	90-d Dietary	NOAEL = 50 mg a.i./kg dw	681	0.07	High

Organism	Exposure	Endpoint value	EEC	MOS	Risk*
	Reproduction	NOAEL = 29 mg a.i./kg bw/d (300 mg a.i./kg dw)	681	0.44	Moderate
Mouse	Dietary	NOAEL = 9.2 mg/kg bw/d (50 mg a.i./kg dw)	677	0.07	High

* Risk characterization: MOS < 0.001 extremely high risk; 0.01–0.001 very high risk; 0.1–0.01 high risk; 1–0.1 moderate risk; 10–1 low risk; >10 negligible risk.

Table 9 Risk to terrestrial organisms—Cabrio EG

Organism	Exposure	Endpoint value	EEC	MOS	Risk*
Invertebrates					
Earthworm	Acute	NOEC = 151 mg a.i./kg soil	0.49 mg a.i./kg soil	308	Negligible
Bee	Contact	NOEC =>112 kg a.i./ha	1350 g a.i./ha	93	Negligible
Birds					
Bobwhite quail	Acute	NOEC = 500 mg a.i./kg bw	210		26 days to reach NOEC
	Dietary	NOEC = 2500 mg a.i./kg dw	210	12	Negligible
	Reproduction	NOAEC = 1062 mg a.i./kg dw	210	5	Low
Mallard duck	Dietary	NOEC = 625 mg a.i./kg dw	41	15	Negligible
	Reproduction	NOAEC = 1061.5 mg a.i./kg dw	41	26	Negligible

Organism	Exposure	Endpoint value	EEC	MOS	Risk*
Mammals					
Rat	Acute	LD_{50} = 5000 mg a.i./kg bw	605		Need 48 d to reach the LD_{50}
	90-d Dietary	NOAEL = 3.5 mg/kg bw/d (50 mg a.i./kg dw)	605	0.08	High
	Reproduction	NOAEL = 29 mg a.i./kg bw/d (300 mg a.i./kg dw)	605	0.5	Moderate
Mouse	Dietary	NOAEL = 9.2 mg/kg bw/d (50 mg a.i./kg dw)	602	0.08	High

* Risk characterization: MOS < 0.001 extremely high risk; 0.01–0.001 very high risk; 0.1–0.01 high risk; 1–0.1 moderate risk; 10–1 low risk; >10 negligible risk.

Appendix V Efficacy Summaries

Table 1 Summary results of the efficacy review for Headline EC

Accepted		
Crop/disease	**Uses**	**Comments**
Chick peas		
Ascochyta blight	2 applications 100–150 g a.i./ha at 10–14 DBA	Aerial and ground applications. For aerial application use only the high rate in 50 L water/ha.
Dry beans (Phaseolus sp.[1], Vigna sp.[2], Lupinus sp.[3], faba beans[4])		
Anthracnose[1, 2]	2 applications 100 g a.i./ha at 10–14 DBA	Aerial and ground applications.
Rust[1]		
Mycosphaerella blight[2, 3, 4]		
Powdery mildew [1, 2, 3, 4]		
Dry field peas		
Mycosphaerella blight	2 applications 100 g a.i./ha at 10–14 DBA.	Aerial and ground applications.
Powdery mildew		
Lentils		
Ascochyta blight	2 applications 100 g a.i./ha at 10–14 DBA.	Aerial and ground applications.
Anthracnose		
Potatoes		
Late blight	6 applications 112–225 g a.i./ha at 5–7 DBA in a minimum of 200 L/ha	Ground application only. For late blight do not make more than one application of Headline EC before alternating to a fungicide with a different mode of action. For early blight apply a maximum of two sequential sprays followed by at least one spray of non-QoI fungicides.
Early blight	6 applications 112–168 g a.i./ha at 7–14 DBA in a minimum of 200 L/ha	

Accepted		
Crop/disease	**Uses**	**Comments**
Sugar beets		
Cercospora leaf spot	4 applications 168–225 g a.i./ha at 14 DBA in 200 L water/ha	No more than 2 sequential applications then alternate to a fungicide with a different mode of action.
Powdery mildew		
Barley		
Spot blotch	2 applications 100–150 g a.i./ha at 10–14 DBA	Aerial and ground applications.
Net blotch		
Scald		
Stripe rust		
Rye		
Leaf rust	2 applications 100–150 g a.i./ha at 10–14 DBA	Aerial and ground applications.
Powdery mildew		
Wheat		
Spot blotch	2 applications 100–150 g a.i./ha at 10–14 DBA	Aerial and ground applications.
Powdery mildew		
Leaf rust		
Tan spot		
Septoria leaf spot		
Stripe rust		
Grass grown for seed (bluegrasses, fescues and ryegrasses only)		
Stem and leaf rust	2 applications 100–168 g a.i./ha at 14–21 DBA	A maximum of 2 applications per season is recommended. Ground application only.
Powdery mildew (suppression)		

Table 2 **Summary results of the value review for Cabrio EG**

Accepted		
Crop/disease	**Use**	**Comments**
Blueberry (highbush and lowbush)		
Anthracnose	4 applications 200 g a.i./ha at 10–14 DBA	No more than two sequential applications then alternate to a fungicide with a different mode of action.
Phomopsis		
Bulb Vegetables Group: Onions (dry and green), garlic, leek and shallot		
Alternaria purple blotch	3 applications 112–168 at 7–14 DBA	No more than two sequential applications then alternate to a fungicide with a different mode of action.
Downy mildew	3 applications 112–168 at 10 DBA	
Cucurbit Vegetables: field cucumber, gherkin, muskmelon, citron melon, watermelon, summer squash, winter squash and pumpkin only.		
Alternaria blight	4 applications 112–168 g a.i./ha at 7 DBA	A maximum of four applications per crop and no sequential applications are recommended by the NAQoI
Anthracnose		
Downy mildew	4 applications 112–168 g a.i./ha at 7 DBA	
Gummy stem blight	4 applications 168 g a.i./ha at 7 DBA	
Powdery mildew	4 applications 112–168 g a.i./ha at 7–14 DBA	
Fruiting Vegetables: Field tomato, field peppers (bell, chilli, cooking, sweet, pimento), and eggplant only.		
Anthracnose	6 applications at 112–168 g a.i./ha at 7–14 DBA	NAQoI recommends a maximum of six applications per season and a maximum of two sequential sprays followed by a fungicide with a different mode of action. For late blight, follow each application of Cabrio EG with a fungicide with a different mode of action.
Late blight on tomato and eggplant only	6 applications 112–200 g a.i./ha at 7 DBA	
Early blight	6 applications 112–168 g a.i./ha at 7–14 DBA	

Accepted		
Crop/disease	**Use**	**Comments**
Root Vegetables: Carrot, garden beet, turnip, rutabaga, oriental radish, radish, and horseradish only		
Alternaria	3 applications 112–224 g a.i./ha at 7–14 DBA	No more than 2 sequential applications then alternate to a fungicide with a different mode of action.
Cercospora	3 applications 112–168 g a.i./ha at 7–14 DBA	
Powdery mildew	3 applications 112–168 g a.i./ha at 7 DBA	
Stone Fruits Group 12: Apricot, cherries (sweet and tart), nectarine, peach, plums, and prune		
Anthracnose	5 applications at 134 g a.i./ha at 7–14 DBA	No more than two sequential applications then alternate to a fungicide with a different mode of action.
Monilinia blossom and twig blight Suppression only		
Powdery mildew on cherries (sweet and tart) only		
Strawberry		
Anthracnose	5 applications 112–200 g a.i./ha at 7–14 DBA	No more than two sequential applications then alternate to a fungicide with a different mode of action.

Table 3 Alternative fungicide products

Crop	Pests	Available alternative active ingredient
Headline EC		
Barley	Spot blotch, net blotch, scald, stripe rust	Propiconazole, carbathiin, maneb + thiram, triadimenol
Rye	Leaf rust, powdery mildew	None registered
Wheat	Spot blotch, powdery mildew, rust, stripe rust, septoria leaf spot, tan spot	Chlorothalonil, mancozeb, propiconazole, triadimenol
Lentils	Ascochyta blight, anthracnose	Chlorothalonil, mancozeb, carbathiin + thiabendazole

Crop	Pests	Available alternative active ingredient
Field peas	Mycosphaerella blight, powdery mildew	Chlorothalonil, sulphur
Beans	Anthracnose, rust	Copper sulphate, thiophanate-methyl
	Mycosphaerella blight, powdery mildew	None registered
Chick peas	Ascochyta blight	Chlorothalonil, carbathiin + thiabendazole
Potatoes	Late blight, early blight	Chlorothalonil, mancozeb, metiram, propamocarb hydrochloride, metalaxyl-M
Sugar beets	Cercospora leaf spot, powdery mildew	Metiram, mancozeb, copper hydroxide
Bluegrasses, fescues, ryegrass	Stem rust, leaf rust, powdery mildew	Myclobutanil, propiconazole,
Cabrio EG		
Blueberries	Anthracnose, phomopsis	Anilazine, chlorothalonil
Bulb vegetables group	Alternaria purple blotch, downy mildew	Anilazine, fosetyl-al, iprodione, maneb, mancozeb, metalaxyl-M + mancozeb, zineb
Field cucumber, muskmelon, watermelon, winter squash, pumpkin and summer squash	Alternaria blight, anthracnose, downy mildew, powdery mildew, gummy stem blight	Benomyl, captan, chlorothalonil, copper oxychloride, copper sulphate, iprodione, maneb, ziram
Field tomato, field peppers (bell, chilli, cooking, sweet, pimento), eggplant	Anthracnose, late blight, early blight	Captan, chlorothalonil, copper oxychloride, copper sulphate, mancozeb, maneb, metiram, zineb, ziram
Carrots, garden beet, radish, oriental radish, turnip, rutabaga, horseradish	Alternaria, cercospora, powdery mildew	Chlorothalonil, copper sulphate, mancozeb, maneb, metiram, zineb
Stone fruits group	Anthracnose, monilinia blossom and twig blight, powdery mildew on cherries only	Benomyl, cyprodinil, tri-basic copper sulphate, ferbam, iprodione, myclobutanil, propiconazole, sulphur, triforine
Strawberries	Anthracnose	Benomyl

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